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(54) Title: NOVEL DIAGNOSTIC AGENTS OF CHRONIC OR PERSISTENT CHLAMYDIAL DISEASES AND USES THEREOF

(57) Abstract: The present invention discloses compositions and methods for detecting organisms of the Chlamydiaceae family, including species of Chlamydia and Chlamydophila, in the persistent phase of their developmental cycle and for the diagnosis of chronic or persistent infections caused by such organisms. The present invention also discloses methods for screening agents that are useful inter alia for modulating a gene whose expression is altered in the persistent phase of the chlamydial developmental cycle or for modulating the level and/or functional activity of an expression product of that gene. Also disclosed are methods and compositions for the treatment and/or prophylaxis of infections, including chronic infections, caused by chamydial organisms using the aforesaid modulatory agents and optionally agents that are effective in modulating the expression of a gene associated with the lytic phase of said developmental cycle or in modulating the level and/or functional activity of an expression product of that gene. The invention also discloses methods and compositions for the treatment and/or prophylaxis of such infections using a first immunopotentiating agent that elicits the production of elements that are immuno-interactive with an antigen associated with the persistent phase of the chlamydial developmental cycle and a second immunopotentiating agent that elicits the production of elements that are immuno-interactive with an antigen associated with the lytic phase of said developmental cycle.

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NOVEL DIAGNOSTIC AGENTS AND USES THEREFOR

FIELD OF THE INVENTION

THIS INVENTION relates generally to infections caused by organisms belonging to the family Chlamydiaceae. More particularly, the present invention relates to the detection of organisms of the Chlamydiaceae family, including species of *Chlamydia* and *Chlamydophila*, in the persistent phase of their developmental cycle and to the diagnosis of chronic or persistent infections caused by such organisms. The present invention also extends to the development of methods for screening agents that are useful *inter alia* for modulating a gene whose expression is altered in the persistent phase of said developmental cycle or for modulating the level and/or functional activity of an expression product of that gene. The invention also encompasses the treatment and/or prophylaxis of infections, including chronic infections, caused by said organisms using the aforesaid modulatory agents and optionally agents that are effective in modulating the expression of a gene associated with the lytic phase of said developmental cycle or in modulating the level and/or functional activity of an expression product of that gene. The invention also extends to the treatment and/or prophylaxis of such infections using a first immunopotentiating agent that elicits the production of elements that are immuno-interactive with an antigen associated with the persistent phase of said developmental cycle and a second immunopotentiating agent that elicits the production of elements that are immuno-interactive with an antigen associated with the lytic phase of said developmental cycle.

Bibliographic details of the publications referred to in this specification are collected at the end of the description.

BACKGROUND OF THE INVENTION

The chlamydiae are important pathogens of humans, birds and a wide range of animals. They primarily cause disease at mucosal sites, such as the eye (trachoma), the female urogenital tract (tubal blockage and infertility in humans, abortion in animals) and

the lungs (pneumonia, chronic obstructive pulmonary disease). They can also be found associated with more systemic diseases such as psittacosis and have recently been implicated in atherosclerosis. Many of the disease states caused by chlamydial infection are primarily not due to the initial lytic insult of the parasite but progress slowly over many years (eg. trachoma, tubal infertility). It has been suggested therefore that the pathogenesis of chlamydial infections is due to a host initiated hypersensitivity response to specific chlamydial antigens, resultant from chronic low grade chlamydial infection (Morrison *et al.*, 1989). While there is some data from the late 1980s to implicate chlamydial heat shock 60 protein in this immune mediated pathogenesis (Morrison *et al.*, 1989), this has not been well replicated and it appears likely that additional chlamydial antigens are involved.

Phylogenetically, the chlamydiae are a unique group of bacteria, characterised by a developmental cycle that involves the conversion between two distinct morphological forms. Infection begins with the attachment of the infectious elementary body (EB) to a susceptible eukaryotic cell and subsequent ingestion into a host-derived endosome. Inside this developing chlamydial inclusion, the EB differentiates into the non-infectious reticulate body (RB), which multiplies by binary fission an estimated 200-300-fold (Mathews *et al.*, 1999). After 48-72 hours (depending on the chlamydial species and strain) the RBs reorganise back into metabolically inactive but infectious EBs, which are subsequently released upon host cell lysis. While this lytic developmental cycle is well characterised *in vitro*, recent evidence supports the presence of an additional, non-lytic, persistent phase of the cycle. Various authors have reported the induction of morphologically abnormal, persistent or chronic forms of chlamydiae induced by such agents as β-lactam antibiotics, D-cycloserine, IFN-δ or nutrient deprivation (Beatty *et al.*, 1993a; Coles *et al.*, 1993; Kramer & Gordon, 1971; Matsumoto & Manire, 1970). These persistent chlamydial forms are characterised by altered morphology (usually enlarged with aberrant shape), by being viable but non-infectious when passaged to other cells and by having altered steady-state levels of some chlamydial antigens (MOMP, OMPcB, LPS, HSP60). These persistent chlamydiae apparently are not end-stage forms that are on an irreversible path to death, as they can be reactivated by several means including removal of the IFN-δ or addition of tryptophan (Beatty *et al.*, 1995). A recent report by Harper *et al.* (2000) suggests that metabolic starvation (low levels of amino acids and even glucose) results in *C. trachomatis* switching some of its growth to the morphologically abnormal

persistent phase, and that this stress state might be a common feature of all persistent stages, induced by many different types of upstream initiators. Harper *et al.* (2000) go further to suggest that the normal developmental cycle for *Chlamydia* might only be representative of the organism growing under ideal *in vitro* conditions and that many *in vivo* conditions could result in metabolic stress causing at least some of the organisms to switch to the persistent state.

SUMMARY OF THE INVENTION

The present inventors have surprisingly discovered that, in addition to genes encoding MOMP, OMPcB and HSP60 (*ompA*, *ompB* and *hsp60*) and genes involved in the biosynthesis of LPS, there are at least three other chlamydial genes, including *pyk*, *nlpD* and *Cpn0585*, whose steady-state expression is altered in the persistent phase of the chlamydial developmental cycle. It is believed that the expression of other chlamydial genes may also be altered in the persistent phase, particularly those genes involved in the same regulatory or biosynthetic pathways as *pyk*, *nlpD*, *Cpn0585*, *ompA*, *ompB*, *hsp60* or as a gene involved in the biosynthesis of LPS. The identification of these target genes permits the selection or rational design of agents that modulate the expression of the those genes or the level and/or functional activity of their expression products for use *inter alia* in the prevention and/or treatment of infections, including persistent or chronic infections, caused by an organism of the Chlamydiaceae family.

Accordingly, in one aspect of the present invention, there is provided a method for detecting an organism of the Chlamydiaceae family in the persistent phase of its developmental cycle, said method comprising detecting, relative to the lytic phase of said developmental cycle, a change in the level and/or functional activity of an expression product of a gene selected from *pyk*, *nlpD*, *Cpn0585*, or a gene belonging to the same regulatory or biosynthetic pathway as *pyk*, *nlpD*, *Cpn0585*, *ompA*, *ompB*, *hsp60* or as a gene involved in the biosynthesis of LPS, or a variant of said gene.

Preferably, the change is an at least 10%, more preferably at least 50%, even more preferably at least 100%, even more preferably at least 200%, even more preferably at least 400%, even more preferably at least 600% and still even more preferably at least 1000% change in said level and/or functional activity.

In another aspect, the invention contemplates a method for detecting an organism of the Chlamydiaceae family in the persistent phase of its developmental cycle, said method comprising detecting, relative to the lytic phase of said developmental cycle, a change in the level and/or functional activity of an expression product of a gene selected from *pyk*, *nlpD*, *Cpn0585* or a gene belonging to the same regulatory or biosynthetic pathway as *pyk*, *nlpD* or *Cpn0585*, or a variant of said gene.

In yet another aspect, the invention encompasses a method for diagnosis of a persistent or chronic infection in a patient, wherein said infection is caused by an organism of the Chlamydiaceae family, said method comprising detecting in a biological sample obtained from said patient, relative to the lytic phase of the developmental cycle of said organism, a change in the level and/or functional activity of an expression product of a gene selected from *pyk*, *nlpD*, *Cpn0585*, or a gene belonging to the same regulatory or biosynthetic pathway as *pyk*, *nlpD*, *Cpn0585*, *ompA*, *ompB*, *hsp60* or as a gene involved in the biosynthesis of LPS, or a variant of said gene.

In still yet another aspect, the invention features a method for diagnosis of a persistent or chronic infection in a patient, wherein said infection is caused by an organism of the Chlamydiaceae family, said method comprising detecting in a biological sample obtained from said patient, relative to the lytic phase of the developmental cycle of said organism, a change in the level and/or functional activity of an expression product of a gene selected from *pyk*, *nlpD*, *Cpn0585*, or a gene belonging to the same regulatory or biosynthetic pathway as *pyk*, *nlpD* or *Cpn0585*, or a variant of said gene.

In one embodiment, the method preferably comprises:

– contacting the biological sample with an antigen-binding molecule that is immuno-interactive with a polypeptide expressed from said gene;

– measuring the concentration of a complex comprising said polypeptide and the antigen binding molecule in said contacted sample; and

– relating said measured complex concentration to the concentration of said polypeptide in said sample.

Preferably, the concentration of said polypeptide in said biological sample is compared to a reference level of said polypeptide corresponding to said lytic phase.

In another embodiment, the method preferably comprises:

– measuring the level of a transcript expressed from said gene in said biological sample.

Preferably, the level of said transcript in said biological sample is compared to a reference level of said transcript corresponding to said lytic phase.

In yet another embodiment, the method preferably comprises:

– contacting the biological sample with an antigen corresponding to at least a portion of a polypeptide encoded by said gene;

– measuring the concentration of a complex comprising said antigen and an antigen-binding molecule in said contacted sample; and

– relating said measured complex concentration to the concentration of antigen-binding molecule in said sample to thereby determine the amount or level of said polypeptide in said sample.

Preferably, the concentration of said antigen-binding molecule in said biological sample is compared to a reference level of said antigen-binding molecule corresponding to said lytic phase.

In still yet another embodiment, the method preferably comprises:

– contacting the biological sample with an antigen corresponding to at least a portion of a polypeptide encoded by said gene;

– measuring the level of antigen-specific T cell proliferation in said contacted sample to thereby determine the amount or level of said polypeptide in said sample.

Preferably, the level of said antigen-specifc T cell proliferation in said biological sample is compared to a reference level of antigen-specifc T cell proliferation corresponding to said lytic phase.

In a further aspect, the invention extends to a method of screening for an agent that modulates the expression of a gene or the level and/or functional activity of an expression product of said gene, wherein said gene is selected from *pyk*, *nlpD*, *Cpn0585*, or a gene belonging to the same regulatory or biosynthetic pathway as *pyk*, *nlpD*,

Cpn0585, *ompA*, *ompB*, *hsp60* or as a gene involved in the biosynthesis of LPS, or a variant of said gene, said method comprising:

– contacting a preparation comprising a polypeptide encoded by said gene, or biologically active fragment of said polypeptide, or variant or derivative of these, or a genetic sequence that modulates the expression of said gene, with a test agent; and

– detecting a change in the level and/or functional activity of said polypeptide or biologically active fragment thereof, or variant or derivative, or of a product expressed from said genetic sequence.

In yet a further aspect, the invention resides in a method of screening for an agent that modulates the expression of a gene or the level and/or functional activity of an expression product of said gene, wherein said gene is selected from *pyk*, *nlpD*, *Cpn0585*, or a gene belonging to the same regulatory or biosynthetic pathway as *pyk*, *nlpD* or *Cpn0585*, or a variant of said gene, said method comprising:

– contacting a preparation comprising a polypeptide encoded by said gene, or biologically active fragment of said polypeptide, or variant or derivative of these, or a genetic sequence that modulates the expression of said gene, with a test agent; and

– detecting a change in the level and/or functional activity of said polypeptide or biologically active fragment thereof, or variant or derivative, or of a product expressed from said genetic sequence.

In still yet a further aspect, the invention provides a composition for treatment and/or prophylaxis of chronic infection caused by an organism of the Chlamydiaceae family, comprising an agent as broadly described above, together with a pharmaceutically acceptable carrier and/or diluent.

In another aspect, the invention contemplates a method of modulating the expression of a gene or the level and/or functional activity of an expression product of said gene, wherein said gene is selected from *pyk*, *nlpD*, *Cpn0585*, or a gene belonging to the same regulatory or biosynthetic pathway as *pyk*, *nlpD*, *Cpn0585*, *ompA*, *ompB*, *hsp60* or as a gene involved in the biosynthesis of LPS, or a variant of said gene, said method comprising contacting a cell containing said gene with an agent for a time and under

conditions sufficient to modulate the expression of said gene or the level and/or functional activity of said expression product.

In yet another aspect, the invention extends to a method of modulating the expression of a gene or the level and/or functional activity of an expression product of said gene, wherein said gene is selected from *pyk*, *nlpD*, *Cpn0585*, or a gene belonging to the same regulatory or biosynthetic pathway as *pyk*, *nlpD* or *Cpn0585*, or a variant of said gene, said method comprising contacting a cell containing said gene with an agent for a time and under conditions sufficient to modulate the expression of said gene or the level and/or functional activity of said expression product.

According to another aspect of the invention, there is provided a method for treatment and/or prophylaxis of a chronic infection caused by an organism of the Chlamydiaceae family in a patient, said method comprising administering to said patient an effective amount of an agent that modulates the expression of a gene or the level and/or functional activity of an expression product of said gene, wherein said gene is selected from *pyk*, *nlpD*, *Cpn0585*, or a gene belonging to the same regulatory or biosynthetic pathway as *pyk*, *nlpD*, *Cpn0585*, *ompA*, *ompB*, *hsp60* or as a gene involved in the biosynthesis of LPS, or a variant of said gene for a time and under conditions sufficient to treat and/or prevent said infection.

In yet another aspect, the invention contemplates a method for treatment and/or prophylaxis of a chronic infection caused by an organism of the Chlamydiaceae family in a patient, said method comprising administering to said patient an effective amount of an agent that modulates the expression of a gene or the level and/or functional activity of an expression product of said gene, wherein said gene is selected from *pyk*, *nlpD*, *Cpn0585*, or a gene belonging to the same regulatory or biosynthetic pathway as *pyk*, *nlpD* or *Cpn0585*, or a variant of said gene for a time and under conditions sufficient to treat and/or prevent said infection.

Still another aspect of the present invention encompasses a method for treatment and/or prophylaxis of a lytic or chronic infection caused by an organism of the Chlamydiaceae family in a patient, said method comprising sequentially or simultaneously administering to said patient effective amounts of a first agent and a second agent for a

time and under conditions sufficient to treat and/or prevent said infection, wherein said first agent modulates the expression of a first gene expressed in the persistent phase of the developmental cycle of said organism or the level and/or functional activity of an expression product of said first gene, and wherein said second agent modulates the expression of a second gene expressed in the lytic phase of said developmental cycle or the level and/or functional activity of an expression product of said second gene.

In a preferred embodiment, the first gene is selected from *pyk*, *nlpD*, *Cpn0585*, *ompA*, *ompB*, *hsp60* or a gene involved in the biosynthesis of LPS, or a gene belonging to the same regulatory or biosynthetic pathway as *pyk*, *nlpD*, *Cpn0585*, *ompA*, *ompB*, *hsp60* or said gene involved in the biosynthesis of LPS, or a variant of these.

In an especially preferred embodiment, the first gene is selected from *pyk*, *nlpD* or *Cpn0585*, or a gene belonging to the same regulatory or biosynthetic pathway as *pyk*, *nlpD* or *Cpn0585*.

In another embodiment, the second agent is an antibiotic effective in treating and/or preventing said lytic infection.

In another embodiment, the second agent is immuno-interactive with an antigen expressed in the lytic phase of said developmental cycle.

Still yet another aspect of the present invention features a method for treatment and/or prophylaxis of a lytic or chronic infection caused by an organism of the Chlamydiaceae family in a patient, said method comprising sequentially or simultaneously administering to said patient an effective amount of a first agent that modulates the expression of a first gene expressed in the persistent phase of the developmental cycle of said organism, or the level and/or functional activity of an expression product of said first gene, for a time and under conditions sufficient to cause said organism to enter the lytic phase of said developmental cycle, together with an effective amount of a second agent that modulates the expression of a second gene associated with the lytic phase of said developmental cycle or the level and/or functional activity of an expression product of said second gene, for a time and under conditions sufficient to kill, attenuate or otherwise inactivate said organism.

Still a further aspect of the present invention envisions a method for treatment and/or prophylaxis of a lytic or chronic infection caused by an organism of the Chlamydiaceae family in a patient, said method comprising sequentially or simultaneously administering to said patient effective amounts of a first immunopotentiating agent and a second immunopotentiating agent for a time and under conditions sufficient to treat and/or prevent said infection, said first immunopotentiating agent being selected from a first proteinaceous molecule comprising at least a portion of a polypeptide, or variant or derivative thereof, associated with the persistent phase of the developmental cycle of said organism, or a polynucleotide from which said first proteinaceous molecule is expressed, said second immunopotentiating agent being selected from a second proteinaceous molecule comprising at least a portion of a polypeptide, or a variant or derivative thereof, associated with the lytic phase of said developmental cycle, or a polynucleotide from which said second proteinaceous molecule is expressed.

In yet another aspect of the present invention there is provided a method for treatment and/or prophylaxis of a lytic or chronic infection caused by an organism of the Chlamydiaceae family in a patient, said method comprising sequentially or simultaneously administering to said patient effective amounts of a first antigen associated with the persistent phase of the developmental cycle of said organism, and a second associated with the lytic phase of said developmental cycle.

In another aspect, the invention provides an immunopotentiating composition for use in treating or preventing a chronic infection caused by an organism of the Chlamydiaceae family, comprising an antigen associated with the persistent phase of the developmental cycle of said organism, together with a pharmaceutically acceptable carrier and/or diluent.

Suitably, said composition further comprises an adjuvant. Preferably, the adjuvant is a mucosal adjuvant.

Suitably, the composition further comprises at least one additional antigen. The additional antigen(s) may be selected from other antigens associated with the persistent phase of said developmental cycle or from of antigens associated with the lytic phase of said developmental cycle.

The antigen may be in the form of a full-length polypeptide, which is expressed by said organism, or a biologically active fragment thereof, or variant or derivative of these.

In still yet another aspect, the invention envisions an immunopotentiating composition for use in treating or preventing a chronic infection caused by an organism of the Chlamydiaceae family, comprising a first antigen associated with the persistent phase of the developmental cycle of said organism and a second antigen associated with the lytic phase of said developmental cycle, together with a pharmaceutically acceptable carrier and/or diluent.

In another aspect, the invention extends to use of at least one antigen associated with the persistent phase of the developmental cycle of an organism of the Chlamydiaceae family in the manufacture of a medicament for treating and/or preventing chronic chlamydial infection in a patient.

In yet another aspect, the invention contemplates use of at least one antigen associated with the persistent phase of the developmental cycle of an organism of the Chlamydiaceae family together with at least one antigen associated with the lytic phase of said developmental cycle in the manufacture of a medicament for treating and/or preventing chlamydial infection in a patient.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1: Transmission electron micrographs of *C. pneumoniae* IOL-207 infected HEp2 cell cultures either (a) untreated (EB, elementary body; RB, reticulate body; IB intermediate body); or (b) treated with IFN-δ (→) indicates pleomorphic RBs (AB, aberrant body) exhibiting abnormal budding/branching.

Figure 2: RT-PCR analysis of gene transcript levels in normal (N) and IFN-δ-treated (IFN-gamma) *C. pneumoniae* cell cultures. Panel A shows an ethidium bromide stained gel for the highly transcribed genes 16SrRNA (equal between N and IFN treatments) versus *ompA* (upregulated in IFN treated cultures). Panel B shows an autoradiograph for analysis of the lower level gene transcripts from *Cpn0585* (upregulated in normal compared to IFN-δ-treated cultures) again using 16SrRNA as an internal control.

Figure 3: RT-PCR analysis of gene transcript levels in normal (N) and IFN-δ-treated (IFN-gamma) *C. pneumoniae* cell cultures for all 14 genes analysed. Genes with unaltered levels of transcription are indicated with an asterisk (*) while those that are upregulated in IFN-δ-treated cultures (persistent) are indicated by <u>underlining</u>.

BRIEF DESCRIPTION OF THE SEQUENCES: SUMMARY TABLE

TABLE A

SEQUENCE ID NUMBER	SEQUENCE	LENGTH
SEQ ID NO: 1	Polynucleotide corresponding to the *Cpn0585* gene of *C. pneumoniae*	2019 nts
SEQ ID NO: 2	Polypeptide sequence encoded by the polynucleotide depicted in SEQ ID NO: 1	672 aa
SEQ ID NO: 3	Polynucleotide sequence corresponding to the *nlpD* gene of *C. pneumoniae*	738 nts
SEQ ID NO: 4	Polypeptide sequence encoded by the polynucleotide sequence of SEQ ID NO: 3	245 aa
SEQ ID NO: 5	Polynucleotide sequence corresponding to the *ompA* gene of *C. pneumoniae*	1185 nts
SEQ ID NO: 6	Polypeptide sequence encoded by the polynucleotide sequence of SEQ ID NO: 5	394 aa
SEQ ID NO: 7	Polynucleotide sequence corresponding to the *ompB* gene of *C. pneumoniae*	1047 nts
SEQ ID NO: 8	Polypeptide sequence encoded by the polynucleotide sequence of SEQ ID NO: 7	348 aa
SEQ ID NO: 9	Polynucleotide sequence corresponding to the *pyk* gene of *C. pneumoniae*	1461 nts
SEQ ID NO: 10	Polypeptide sequence encoded by the polynucleotide sequence of SEQ ID NO: 9	486 aa
SEQ ID NO: 11	Polynucleotide sequence corresponding to the omcB/*ompB* gene of *C. trachomatis* D	1665 nts
SEQ ID NO: 12	Polypeptide sequence encoded by the polynucleotide sequence of SEQ ID NO: 11	554 aa
SEQ ID NO: 13	Polynucleotide sequence corresponding to the *ompA* gene of *C. trachomatis* D	1203 nts

SEQUENCE ID NUMBER	SEQUENCE	LENGTH
SEQ ID NO: 14	Polypeptide sequence encoded by the polynucleotide sequence of SEQ ID NO: 13	400 aa
SEQ ID NO: 15	Polynucleotide sequence corresponding to the *nlpD* gene of *C. trachomatis* D	768 nts
SEQ ID NO: 16	Polypeptide sequence encoded by the polynucleotide sequence of SEQ ID NO: 15	255 aa
SEQ ID NO: 17	Polynucleotide sequence corresponding to the *pyk* gene of *C. trachomatis* D	1494 nts
SEQ ID NO: 18	Polypeptide sequence encoded by the polynucleotide sequence of SEQ ID NO: 17	497 aa
SEQ ID NO: 19	Polynucleotide sequence corresponding to the *ompA* gene of *C. trachomatis* MoPn	1161 nts
SEQ ID NO: 20	Polypeptide sequence encoded by the polynucleotide sequence of SEQ ID NO: 19	387 aa
SEQ ID NO: 21	Polynucleotide sequence corresponding to the *pyk* gene of *C. trachomatis* MoPn	1443 nts
SEQ ID NO: 22	Polypeptide sequence encoded by the polynucleotide sequence of SEQ ID NO: 21	481 aa
SEQ ID NO: 23	Polynucleotide sequence corresponding to the omcB/*ompB* gene of *C. trachomatis* MoPn	1662 nts
SEQ ID NO: 24	Polypeptide sequence encoded by the polynucleotide sequence of SEQ ID NO: 23	554 aa
SEQ ID NO: 25	Polynucleotide sequence corresponding to the *nlpD* gene of *C. trachomatis* MoPn	729 nts
SEQ ID NO: 26	Polypeptide sequence encoded by the polynucleotide sequence of SEQ ID NO: 25	243 aa
SEQ ID NO: 27	Polynucleotide sequence corresponding to the *ompA* gene of *C. pneumoniae* AR039.	1167 nts
SEQ ID NO: 28	Polypeptide sequence encoded by the polynucleotide sequence of SEQ ID NO: 27	389 aa

SEQUENCE ID NUMBER	SEQUENCE	LENGTH
SEQ ID NO: 29	Polynucleotide sequence corresponding to the omcB/*ompB* gene of *C. pneumoniae* AR039	1668 nts
SEQ ID NO: 30	Polypeptide sequence encoded by the polynucleotide sequence of SEQ ID NO: 29	556 aa
SEQ ID NO: 31	Polynucleotide sequence corresponding to the *pyk* gene of *C. pneumoniae* AR039	1452 nts
SEQ ID NO: 32	Polypeptide sequence encoded by the polynucleotide sequence of SEQ ID NO: 31	484 aa
SEQ ID NO: 33	Polynucleotide sequence corresponding to the *Cpn0585* gene of *C. pneumoniae* AR039	1953 nts
SEQ ID NO: 34	Polypeptide sequence encoded by the polynucleotide sequence of SEQ ID NO: 33	651 aa
SEQ ID NO: 35	Polynucleotide sequence corresponding to a *nlpD* homologue of *C. pneumoniae* AR039	699 nts
SEQ ID NO: 36	Polypeptide sequence encoded by the polynucleotide sequence of SEQ ID NO: 35	233 aa
SEQ ID NO: 37	Sequence of first mentioned peptide in Example 3	18 aa
SEQ ID NO: 38	Sequence of second mentioned peptide in Example 3	16 aa
SEQ ID NO: 39	Sequence of third mentioned peptide in Example 3	16 aa
SEQ ID NO: 40	Sequence of fourth mentioned peptide in Example 3	16 aa
SEQ ID NO: 41	Ct16S-F2 primer, Table 1	20 nts
SEQ ID NO: 42	Ct16S-R primer, Table 1	20 nts
SEQ ID NO: 43	CpnompA-F primer, Table 1	20 nts
SEQ ID NO: 44	CpnompA-R primer, Table 1	20 nts
SEQ ID NO: 45	CpnompB-F primer, Table 1	20 nts
SEQ ID NO: 46	CpnompB-R primer, Table 1	20 nts
SEQ ID NO: 47	CpnomcB-F primer, Table 1	20 nts

SEQUENCE ID NUMBER	SEQUENCE	LENGTH
SEQ ID NO: 48	CpnomcB-R primer, Table 1	20 nts
SEQ ID NO: 49	Cpn76kDa-F primer, Table 1	30 nts
SEQ ID NO: 50	Cpn76kDa-R primer, Table 1	28 nts
SEQ ID NO: 51	Cpnpmp1-F primer, Table 1	20 nts
SEQ ID NO: 52	Cpnpmp1-R primer, Table 1	20 nts
SEQ ID NO: 53	CpngltX-F primer, Table 1	20 nts
SEQ ID NO: 54	CpngltX-R primer, Table 1	20 nts
SEQ ID NO: 55	Cpnhsp60B-F primer, Table 1	20 nts
SEQ ID NO: 56	Cpnhsp60AI-R primer, Table 1	20 nts
SEQ ID NO: 57	CpnyaeT-F primer, Table 1	20 nts
SEQ ID NO: 58	CpnyaeT-R primer, Table 1	20 nts
SEQ ID NO: 59	Cpnpyk-F primer, Table 1	20 nts
SEQ ID NO: 60	Cpnpyk-R primer, Table 1	20 nts
SEQ ID NO: 61	CpnnlpD-F primer, Table 1	20 nts
SEQ ID NO: 62	CpnnlpD-R primer, Table 1	20 nts
SEQ ID NO: 63	Cpn0585-F primer, Table 1	20 nts
SEQ ID NO: 64	Cpn0585-R primer, Table 1	20 nts
SEQ ID NO: 65	Cpn1046-F primer, Table 1	20 nts
SEQ ID NO: 66	Cpn1046-R primer, Table 1	20 nts

DETAILED DESCRIPTION OF THE INVENTION

1. Definitions

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by those of ordinary skill in the art to which the invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, preferred methods and materials are described. For the purposes of the present invention, the following terms are defined below.

The articles *"a"* and *"an"* are used herein to refer to one or to more than one (i.e. to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element.

By *"agent"* is meant a naturally occurring or synthetically produced molecule which interacts either directly or indirectly with a target member, the level and/or functional activity of which are to be modulated.

"Amplification product" refers to a nucleic acid product generated by nucleic acid amplification techniques.

By *"antigen-binding molecule"* is meant a molecule that has binding affinity for a target antigen. It will be understood that this term extends to immunoglobulins, immunoglobulin fragments and non-immunoglobulin derived protein frameworks that exhibit antigen-binding activity.

By *"associated with the persistent phase"* or *"associated with the lytic phase"* and the like is meant a molecule that is expressed at a higher level and/or functional activity in one of said phases relative to the other of said phases. Suitably, a selected molecule in a particular phase of the chlamydial developmental cycle is associated with that phase if it's level and/or functional activity is at least 110%, more preferably at least 150%, even more preferably at least 200%, even more preferably at least 300%, even more preferably at least 500% and still even more preferably at least 1000% of the level and/or functional activity of that molecule in the other phase of said developmental cycle.

As used herein, the term *"binds specifically"* and the like refers to antigen-binding molecules that bind the polypeptide or polypeptide fragments of the invention but do not significantly bind to homologous prior art polypeptides.

By *"biologically active fragment"* is meant a fragment of a full-length parent polypeptide which fragment retains the activity of the parent polypeptide. As used herein, the term *"biologically active fragment"* includes deletion mutants and small peptides, for example of at least 10, preferably at least 20 and more preferably at least 30 contiguous amino acids, which comprise the above activities. Peptides of this type may be obtained through the application of standard recombinant nucleic acid techniques or synthesised using conventional liquid or solid phase synthesis techniques. For example, reference may be made to solution synthesis or solid phase synthesis as described, for example, in Chapter 9 entitled *"Peptide Synthesis"* by Atherton and Shephard which is included in a publication entitled *"Synthetic Vaccines"* edited by Nicholson and published by Blackwell Scientific Publications. Alternatively, peptides can be produced by digestion of a polypeptide of the invention with proteinases such as endoLys-C, endoArg-C, endoGlu-C and staphylococcus V8-protease. The digested fragments can be purified by, for example, high performance liquid chromatographic (HPLC) techniques.

The term *"biological sample"* as used herein refers to a sample that may be extracted, untreated, treated, diluted or concentrated from an animal. The biological sample may be selected from the group consisting of whole blood, serum, plasma, saliva, urine, sweat, ascitic fluid, peritoneal fluid, synovial fluid, amniotic fluid, cerebrospinal fluid, skin biopsy, and the like. Preferably, the biological sample is selected from a mucosal swab, a sputum sample, a throat swab, an aspirate, a nasopharyngeal aspirate, bronchio-alveolar lavage fluids and blood, including whole blood, serum and plasma.

The term *"chlamydial"* as used herein refers to an element, function, activity, property or feature associated with an organism belonging to the family Chlamydiaceae.

Throughout this specification, unless the context requires otherwise, the words *"comprise"*, *"comprises"* and *"comprising"* will be understood to imply the inclusion of a stated step or element or group of steps or elements but not the exclusion of any other step or element or group of steps or elements.

By "*corresponds to*" or "*corresponding to*" is meant a polynucleotide (a) having a nucleotide sequence that is substantially identical or complementary to all or a portion of a reference polynucleotide sequence or (b) encoding an amino acid sequence identical to an amino acid sequence in a peptide or protein. This phrase also includes within its scope a peptide or polypeptide having an amino acid sequence that is substantially identical to a sequence of amino acids in a reference peptide or protein.

By *"derivative"* is meant a polypeptide that has been derived from the basic sequence by modification, for example by conjugation or complexing with other chemical moieties or by post-translational modification techniques as would be understood in the art. The term "*derivative*" also includes within its scope alterations that have been made to a parent sequence including additions, or deletions that provide for functionally equivalent molecules.

By "*effective amount*", in the context of treating or preventing an infection, preferably a chronic chlamydial infection, is meant the administration of that amount of active to an individual, either in a single dose or as part of a series, that is effective for treatment or prophylaxis of that infection. The effective amount will vary depending upon the health and physical condition of the individual to be treated, the taxonomic group of individual to be treated, the formulation of the composition, the assessment of the medical situation, and other relevant factors. It is expected that the amount will fall in a relatively broad range that can be determined through routine trials.

As used herein, the term *"function"* refers to a biological, enzymatic, or therapeutic function.

"Homology" refers to the percentage number of amino acids that are identical or constitute conservative substitutions as defined in Table A *infra*. Homology may be determined using sequence comparison programs such as GAP (Deveraux *et al.* 1984, *Nucleic Acids Research* **12**, 387-395). In this way, sequences of a similar or substantially different length to those cited herein might be compared by insertion of gaps into the alignment, such gaps being determined, for example, by the comparison algorithm used by GAP. Variant peptides or polypeptides, isolated from a species of a genus belonging to the family Chlamydiaceae, may comprise conservative amino acid substitutions. Exemplary

conservative substitutions in a polypeptide or polypeptide fragment according to the invention are recited the following table:

TABLE B

Original Residue	Exemplary Substitutions
Ala	Ser
Arg	Lys
Asn	Gln, His
Asp	Glu
Cys	Ser
Gln	Asn
Glu	Asp
Gly	Pro
His	Asn, Gln
Ile	Leu, Val
Leu	Ile, Val
Lys	Arg, Gln, Glu
Met	Leu, Ile,
Phe	Met, Leu, Tyr
Ser	Thr
Thr	Ser
Trp	Tyr
Tyr	Trp, Phe
Val	Ile, Leu

"*Hybridisation*" is used herein to denote the pairing of complementary nucleotide sequences to produce a DNA-DNA hybrid or a DNA-RNA hybrid. Complementary base sequences are those sequences that are related by the base-pairing rules. In DNA, A pairs with T and C pairs with G. In RNA U pairs with A and C pairs with G. In this regard, the terms "match" and "mismatch" as used herein refer to the hybridisation potential of paired nucleotides in complementary nucleic acid strands. Matched nucleotides hybridise efficiently, such as the classical A-T and G-C base pair mentioned above. Mismatches are other combinations of nucleotides that do not hybridise efficiently.

Reference herein to *"immuno-interactive"* includes reference to any interaction, reaction, or other form of association between molecules and in particular where one of the molecules is, or mimics, a component of the immune system.

By *"immuno-interactive fragment"* is meant a fragment of a parent polypeptide, which fragment elicits an immune response, including the production of elements that specifically bind to said polypeptide, or variant or derivative thereof. As used herein, the term *"immuno-interactive fragment"* includes deletion mutants and small peptides, for example of at least six, preferably at least 8 and more preferably at least 20 contiguous amino acids, which comprise antigenic determinants or epitopes. Several such fragments may be joined together.

By *"isolated"* is meant material that is substantially or essentially free from components that normally accompany it in its native state. For example, an "isolated polynucleotide", as used herein, refers to a polynucleotide, which has been purified from the sequences which flank it in a naturally occurring state, *e.g.*, a DNA fragment which has been removed from the sequences which are normally adjacent to the fragment.

By *"modulating"* is meant increasing or decreasing, either directly or indirectly, the level and/or functional activity of a target molecule. For example, an agent may indirectly modulate the said level/activity by interacting with a molecule other than the target molecule. In this regard, indirect modulation of a gene encoding a target polypeptide includes within its scope modulation of the expression of a first nucleic acid molecule, wherein an expression product of the first nucleic acid molecule modulates the expression of a nucleic acid molecule encoding the target polypeptide.

By *"obtained from"* is meant that a sample such as, for example, a nucleic acid extract or polypeptide extract is isolated from, or derived from, a particular source of the host. For example, the extract may be obtained from a tissue or a biological fluid isolated directly from the host.

The term *"oligonucleotide"* as used herein refers to a polymer composed of a multiplicity of nucleotide units (deoxyribonucleotides or ribonucleotides, or related structural variants or synthetic analogues thereof) linked via phosphodiester bonds (or related structural variants or synthetic analogues thereof). Thus, while the term "oligonucleotide" typically refers to a nucleotide polymer in which the nucleotides and linkages between them are naturally occurring, it will be understood that the term also includes within its scope various analogues including, but not restricted to, peptide nucleic acids (PNAs), phosphoramidates, phosphorothioates, methyl phosphonates, 2-O-methyl ribonucleic acids, and the like. The exact size of the molecule may vary depending on the particular application. An oligonucleotide is typically rather short in length, generally from about 10 to 30 nucleotides, but the term can refer to molecules of any length, although the term "polynucleotide" or "nucleic acid" is typically used for large oligonucleotides.

By *"operably linked"* is meant that transcriptional and translational regulatory nucleic acids are positioned relative to a polypeptide-encoding polynucleotide in such a manner that the polynucleotide is transcribed and the polypeptide is translated.

The term *"patient"* refers to patients of human or other animals including birds, and includes any individual it is desired to examine or treat using the methods of the invention. However, it will be understood that *"patient"* does not imply that symptoms are present. Suitable mammals that fall within the scope of the invention include, but are not restricted to, primates, livestock animals (*e.g.*, sheep, cows, horses, donkeys, pigs), laboratory test animals (*e.g.*, rabbits, mice, rats, guinea pigs, hamsters), companion animals (*e.g.*, cats, dogs) and captive wild animals (*e.g.*, foxes, deer, dingoes).

By *"pharmaceutically-acceptable carrier"* is meant a solid or liquid filler, diluent or encapsulating substance that may be safely used in topical or systemic administration.

The term "*polynucleotide*" or "*nucleic acid*" as used herein designates mRNA, RNA, cRNA, cDNA or DNA. The term typically refers to oligonucleotides greater than 30 nucleotides in length.

The terms "*polynucleotide variant*" and "*variant*" refer to polynucleotides displaying substantial sequence identity with a reference polynucleotide sequence or polynucleotides that hybridise with a reference sequence under stringent conditions that are defined hereinafter. These terms also encompasses polynucleotides in which one or more nucleotides have been added or deleted, or replaced with different nucleotides. In this regard, it is well understood in the art that certain alterations inclusive of mutations, additions, deletions and substitutions can be made to a reference polynucleotide whereby the altered polynucleotide retains the biological function or activity of the reference polynucleotide. The terms "*polynucleotide variant*" and "*variant*" also include naturally occurring variants such as allelic variants.

"*Polypeptide*", "*peptide*" and "*protein*" are used interchangeably herein to refer to a polymer of amino acid residues and to variants and synthetic analogues of the same. Thus, these terms apply to amino acid polymers in which one or more amino acid residues is a synthetic non-naturally occurring amino acid, such as a chemical analogue of a corresponding naturally occurring amino acid, as well as to naturally-occurring amino acid polymers.

The term "*polypeptide variant*" refers to polypeptides whose sequence is distinguished from a reference polypeptide by substitution, deletion or addition of at least one amino acid. It is well understood in the art that some amino acids may be changed to others with broadly similar properties without changing the nature of the activity of the polypeptide (conservative substitutions) as described above in Table B.

By "*primer*" is meant an oligonucleotide which, when paired with a strand of DNA, is capable of initiating the synthesis of a primer extension product in the presence of a suitable polymerising agent. The primer is preferably single-stranded for maximum efficiency in amplification but may alternatively be double-stranded. A primer must be sufficiently long to prime the synthesis of extension products in the presence of the polymerisation agent. The length of the primer depends on many factors, including

application, temperature to be employed, template reaction conditions, other reagents, and source of primers. For example, depending on the complexity of the target sequence, the oligonucleotide primer typically contains 15 to 35 or more nucleotides, although it may contain fewer nucleotides. Primers can be large polynucleotides, such as from about 200 nucleotides to several kilobases or more. Primers may be selected to be "substantially complementary" to the sequence on the template to which it is designed to hybridise and serve as a site for the initiation of synthesis. By "substantially complementary", it is meant that the primer is sufficiently complementary to hybridise with a target nucleotide sequence. Preferably, the primer contains no mismatches with the template to which it is designed to hybridise but this is not essential. For example, non-complementary nucleotides may be attached to the 5' end of the primer, with the remainder of the primer sequence being complementary to the template. Alternatively, non-complementary nucleotides or a stretch of non-complementary nucleotides can be interspersed into a primer, provided that the primer sequence has sufficient complementarity with the sequence of the template to hybridise therewith and thereby form a template for synthesis of the extension product of the primer.

"Probe" refers to a molecule that binds to a specific sequence or sub-sequence or other moiety of another molecule. Unless otherwise indicated, the term "probe" typically refers to a polynucleotide probe that binds to another nucleic acid, often called the "target nucleic acid", through complementary base pairing. Probes may bind target nucleic acids lacking complete sequence complementarity with the probe, depending on the stringency of the hybridisation conditions. Probes can be labelled directly or indirectly.

The term *"recombinant polynucleotide"* as used herein refers to a polynucleotide formed *in vitro* by the manipulation of nucleic acid into a form not normally found in nature. For example, the recombinant polynucleotide may be in the form of an expression vector. Generally, such expression vectors include transcriptional and translational regulatory nucleic acid operably linked to the nucleotide sequence.

By *"recombinant polypeptide"* is meant a polypeptide made using recombinant techniques, *i.e.*, through the expression of a recombinant polynucleotide.

By *"reporter molecule"* as used in the present specification is meant a molecule that, by its chemical nature, provides an analytically identifiable signal that allows the detection of a complex comprising an antigen-binding molecule and its target antigen. The term "reporter molecule" also extends to use of cell agglutination or inhibition of agglutination such as red blood cells on latex beads, and the like.

Terms used to describe sequence relationships between two or more polynucleotides or polypeptides include "reference sequence", "comparison window", "sequence identity", "percentage of sequence identity" and "substantial identity". A "*reference sequence*" is at least 12 but frequently 15 to 18 and often at least 25 monomer units, inclusive of nucleotides and amino acid residues, in length. Because two polynucleotides may each comprise (1) a sequence (*i.e.*, only a portion of the complete polynucleotide sequence) that is similar between the two polynucleotides, and (2) a sequence that is divergent between the two polynucleotides, sequence comparisons between two (or more) polynucleotides are typically performed by comparing sequences of the two polynucleotides over a "comparison window" to identify and compare local regions of sequence similarity. A "*comparison window*" refers to a conceptual segment of at least 50 contiguous positions, usually about 50 to about 100, more usually about 100 to about 150 in which a sequence is compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned. The comparison window may comprise additions or deletions (*i.e.*, gaps) of about 20% or less as compared to the reference sequence (which does not comprise additions or deletions) for optimal alignment of the two sequences. Optimal alignment of sequences for aligning a comparison window may be conducted by computerised implementations of algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package Release 7.0, Genetics Computer Group, 575 Science Drive Madison, WI, USA) or by inspection and the best alignment (*i.e.*, resulting in the highest percentage homology over the comparison window) generated by any of the various methods selected. Reference also may be made to the BLAST family of programs as for example disclosed by Altschul *et al.*, 1997, *Nucl. Acids Res.* **25**:3389. A detailed discussion of sequence analysis can be found in Unit 19.3 of Ausubel *et al.*, "Current Protocols in Molecular Biology", John Wiley & Sons Inc, 1994-1998, Chapter 15.

The term *"sequence identity"* as used herein refers to the extent that sequences are identical on a nucleotide-by-nucleotide basis or an amino acid-by-amino acid basis over a window of comparison. Thus, a *"percentage of sequence identity"* is calculated by comparing two optimally aligned sequences over the window of comparison, determining the number of positions at which the identical nucleic acid base (*e.g.*, A, T, C, G, I) or the identical amino acid residue (*e.g.*, Ala, Pro, Ser, Thr, Gly, Val, Leu, Ile, Phe, Tyr, Trp, Lys, Arg, His, Asp, Glu, Asn, Gln, Cys and Met) occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the window of comparison (*i.e.*, the window size), and multiplying the result by 100 to yield the percentage of sequence identity. For the purposes of the present invention, *"sequence identity"* will be understood to mean the "match percentage" calculated by the DNASIS computer program (Version 2.5 for windows; available from Hitachi Software engineering Co., Ltd., South San Francisco, California, USA) using standard defaults as used in the reference manual accompanying the software.

"Stringency" as used herein, refers to the temperature and ionic strength conditions, and presence or absence of certain organic solvents, during hybridisation. The higher the stringency, the higher will be the degree of complementarity between immobilised nucleotide sequences and the labelled polynucleotide sequence.

"Stringent conditions" refers to temperature and ionic conditions under which only nucleotide sequences having a high frequency of complementary bases will hybridise. The stringency required is nucleotide sequence dependent and depends upon the various components present during hybridisation. Generally, stringent conditions are selected to be about 10 to 20° C lower than the thermal melting point (T_m) for the specific sequence at a defined ionic strength and pH. The T_m is the temperature (under defined ionic strength and pH) at which 50% of a target sequence hybridises to a complementary probe.

By *"vector"* is meant a nucleic acid molecule, preferably a DNA molecule derived, for example, from a plasmid, bacteriophage, or plant virus, into which a nucleic acid sequence may be inserted or cloned. A vector preferably contains one or more unique restriction sites and may be capable of autonomous replication in a defined host cell including a target cell or tissue or a progenitor cell or tissue thereof, or be integrable with the genome of the defined host such that the cloned sequence is reproducible. Accordingly,

the vector may be an autonomously replicating vector, *i.e.*, a vector that exists as an extrachromosomal entity, the replication of which is independent of chromosomal replication, *e.g.*, a linear or closed circular plasmid, an extrachromosomal element, a minichromosome, or an artificial chromosome. The vector may contain any means for assuring self-replication. Alternatively, the vector may be one which, when introduced into the host cell, is integrated into the genome and replicated together with the chromosome(s) into which it has been integrated. A vector system may comprise a single vector or plasmid, two or more vectors or plasmids, which together contain the total DNA to be introduced into the genome of the host cell, or a transposon. The choice of the vector will typically depend on the compatibility of the vector with the host cell into which the vector is to be introduced. The vector may also include a selection marker such as an antibiotic resistance gene that can be used for selection of suitable transformants. Examples of such resistance genes are well known to those of skill in the art.

As used herein, underscoring or italicising the name of a gene shall indicate the gene, in contrast to its protein product, which is indicated by the name of the gene in the absence of any underscoring or italicising. For example, "*nlpD*" shall mean the *nlpD* gene, whereas "NlpD" shall indicate the protein product of the "*nlpD*" gene.

2. *Method of modulating the level and/or functional activity of a target molecule whose level and/or functional activity is altered in the persistent phase of the chlamydial developmental cycle*

The present invention is predicated in part on the determination that various genes of organisms belonging the Chlamydiaceae family are differentially expressed between the lytic phase and the persistent phase of their developmental cycle. In particular, the present inventors have discovered that several genes are modulated (*e.g.*, upregulated) in the persistent phase, relative to the lytic phase, of the chlamydial developmental cycle. Not wishing to be bound by any one particular theory or mode of operation, the present inventors consider that alterations in the level and/or functional activity of the expression products (*e.g.*, transcripts and polypeptides) of those genes may be implicated in the pathophysiology of persistent or chronic infections caused by chlamydial organisms. Accordingly, it is believed that by modulating the expression of those genes or the level and/or functional activity of their expression products, the chlamydial organisms will switch from the persistent phase to the lytic phase, thereby promoting accessibility to the immune system or to other therapeutic strategies.

The invention, therefore, provides a method of modulating the expression of a gene or the level and/or functional activity of an expression product of said gene, wherein said gene is selected from *pyk*, *nlpD*, *Cpn0585*, or a gene belonging to the same regulatory or biosynthetic pathway as *pyk*, *nlpD*, *Cpn0585*, *ompA*, *ompB*, *hsp60* or as a gene involved in the biosynthesis of lipopolysaccharide (LPS), or a variant of said gene. The method comprises contacting a cell containing said gene with an agent for a time and under conditions sufficient to modulate the expression of said gene or the level and/or functional activity of said expression product. Preferably, the change is an at least 10%, more preferably at least 50%, even more preferably at least 100%, even more preferably at least 200%, even more preferably at least 400%, even more preferably at least 600% and still even more preferably at least 1000% change in said level and/or functional activity.

Any cell is contemplated by the present invention, which contains a polynucleotide from which a transcript or polypeptide of said gene can be expressed. The cell may be selected from a prokaryotic cell including, but not restricted to, a bacterial cell

or a eukaryotic cell such as a yeast cell, an insect cell or an animal cell. The cell is preferably an epithelial cell or cell line that is infected or infectable with an organism of the Chlamydiaceae family. The family Chlamydiaceae has recently been redefined by Everett *et al.* (1999, *International Journal of Systematic Bacteriology* **49**(Part 2): 415-440) and, for all intended purposes, it shall be understood that the species of the invention may be an organism already known to belong to this family or that is identified and characterised in the future to belong to this family. Suitably, the organism belongs to a genus selected from *Chlamydia* and *Chlamydophila*. For example, the organism may be selected from a species including, but not limited to, *Chlamydia trachomatis*, *Chlamydia muridarum*, *Chlamydia suis*, *Chlamydophila pecorum*, *Chlamydophila pneumoniae*, *Chlamydophila psittaci*, *Chlamydophila abortus*, *Chlamydophila caviae*, and *Chlamydophila felis*. Preferably, the species is *Chlamydophila pneumoniae*.

The cell may be obtained from the epithelium of the genital tract, respiratory tract or conjunctiva or from arthritic joints. Alternatively, the cell may be a circulating macrophage, which is suitably infected with a chlamydial species such as *Chlamydophila pneumoniae*, or it may be associated with atherosclerotic plaque tissue from any suitable site (*e.g.*, heart, arteries, veins, brain and periphery) or multiple sclerosis brain tissue.

Suitably, the cell contains a vector comprising a polynucleotide encoding an expression product of said gene, or a biologically active fragment of said expression product, or a variant or derivative of these, and operably linked to a regulatory nucleic acid molecule, which preferably includes a natural transcriptional element (*e.g.*, promoter) relating to said gene. In another embodiment, the cell contains a vector comprising the regulatory polynucleotide relating to said gene operably connected to a polynucleotide encoding a reporter molecule of choice. Alternatively, the cell can be infected with a species of a genus belonging to the family Chlamydiaceae, which naturally or artificially includes said genes.

In accordance with the present invention, the agent modulates the expression of a gene or the level and/or functional activity of an expression product of said gene, wherein said gene is selected from *pyk*, *nlpD*, *Cpn0585*, or a gene belonging to the same regulatory or biosynthetic pathway as *pyk*, *nlpD*, *Cpn0585*, *ompA*, *ompB*, *hsp60* or as a gene involved in the biosynthesis of LPS, or a variant of said gene. Exemplary genes involved in the

biosynthesis of LPS include, but are not restricted to, *gseA*, *kdsB*, *lpxD*, *lpxA*, *lpxC*, *kdsA* and *lpxB*. Preferably, the gene is selected from *pyk*, *nlpD*, *Cpn0585*, or a gene belonging to the same regulatory or biosynthetic pathway as *pyk*, *nlpD* or *Cpn0585*, or a variant of these. More preferably, the gene is selected from *pyk*, *nlpD* or *Cpn0585*, or a variant of these.

The *pyk* gene encodes pyruvate kinase involved in the glycolysis. Exemplary pyruvate kinase (Pyk) polypeptides or variants include, but are not restricted to, CP0677 of *C. pneumoniae* AR39, CPn0097 of *C. pneumoniae* CWL029, Pyk of *C. pneumoniae* J138, CT332 of *C. trachomatis* serovar D and TC0609 of *C. trachomatis* MoPn.

Other glycolytic pathway related genes include, but are not limited to, *mrsA* (encoding phosphomannomutase), *pfkA_1* (encoding fructose 6-phosphate 1-phosphotransferase), *pfkA_2* (encoding fructose 6-phosphate 1-phosphotransferase), *dhnA* (predicted to encode 1,6-fructose biphosphate aldolase), *gapA* (encoding glyceraldehyde-3-phosphate dehydrogenase), *pgk* (encoding phosphoglycerate kinase), *eno* (encoding enolase), *pgmA* (encoding phosphoglycerate mutase), *pgm* (encoding phosphoglucomutase), *pgi* (encoding glucose-6-phosphate isomerase), and *tpiS* (encoding triosephosphate isomerase).

The *Cpn0585* gene encodes a polypeptide with similarity to *C. psittaci* IncA_2, otherwise known as inclusion membrane protein A, which is required for fusion of chlamydial inclusions. Exemplary polypeptides or variants of this type include, but are not restricted to, CP0163 of *C. pneumoniae* AR39, CPn0585, of *C. pneumoniae* CWL029 and CPj0585 of *C. pneumoniae* J138.

Other inclusion membrane related genes linked by pathway to *Cpn0585* include, but are not limited to, *Cpn0186*, *incB* (encoding inclusion membrane protein B) and *incC* (encoding inclusion membrane protein C). Representative examples of IncA polypeptides or variants include CP0581 of *C. pneumoniae* AR39, CPn0186 of *C. pneumoniae* CWL029, CPn0186 of *C. pneumoniae* J138, TC0396 of *C. trachomatis* MoPn and CT119 of *C. trachomatis* serovar D. Representative examples of IncB polypeptides or variants include CP0467 of *C. pneumoniae* AR39, CPn0291 of *C. pneumoniae* CWL029, IncB of *C. pneumoniae* J138, CT232, *C. trachomatis* serovar D and TC0503 of *C. trachomatis*

MoPn. Representative examples of IncC polypeptides or variants include CP0466 of *C. pneumoniae* AR39, CPn0292 of *C. pneumoniae* CWL029 and IncC of *C. pneumoniae* J138.

The *nlpD* gene encodes a polypeptide with significant similarity to the *Listeria welshimeri* p60 invasin associated protein and to CPn0902 nlpD muraminidase (invasin repeat family). Exemplary polypeptides or variants of this type include, but are not restricted to, CP0964 of *C. pneumoniae* AR39, CPn0902 of *C. pneumoniae* CWL029, NlpD of C. *pneumoniae* J138, CT759 of *C. trachomatis* serovar D and TC0140 of *C. trachomatis* MoPn.

Cell envelope- or peptidoglycan synthesis-related genes linked by pathway to *nlpD* include, but are not limited to, *amiA* (encoding N-acetylmuramoyl-L-alanine amidase, *murE* (encoding UDP-N-acetylmuramoylalanyl DAP ligase), *pbp3* (encoding transglycolase/transpeptidase), *yabC* (encoding Pbp2B family methyltransferase), *murA* (encoding UDP-N-acetylglucosamine 1-carboxyvinyltransferase), *dacF* (encoding D-alanyl-D-alanine carboxypeptidase), *pbpB* (encoding PbpP2 transglycolase/transpeptidase), *amiB* (encoding N-acetylmuramoyl-L-Ala amidase), *glmU* (encoding UDP-N-acetylglucosamine pyrophosphorylase), *murF* (encoding UDP-N-acetylmuramoyl DAP ligase), *mraY* (encoding muramoyl-pentapeptide transferase), *murD* (encoding UDP-N-acetylmuramoylalanine-glutamate ligase), *murG* (encoding peptidoglycan transferase), *murC* and *ddlA* (encoding UDP-N-acetylmuramate-alanine ligase and D-Ala-D-Ala ligase, respectively), *glmS* (encoding glucosamine-fructose-6-P aminotransferase) and *murB* (encoding UDP-N-acetylenolpyruvoylglucosamine reductase).

Non-limiting examples of polynucleotide sequences corresponding to the *pyk*, *nlpD*, *Cpn0585*, *ompA* and *ompB* genes of various chlamydial species are set forth in SEQ ID NO: 9, 17, 21 and 31, SEQ ID NO: 3, 15, 25 and 35, SEQ ID NO: 1 and 33, SEQ ID NO: 5, 13, 19 and 27 and SEQ ID NO: 7, 11, 23 and 29, respectively.

Other genes involved in the same regulatory or biosynthetic pathways as those mentioned above may be identified by analysis of target polypeptide – binding partner interactions. Such identification can be carried out, for example, using the yeast Two-

Hybrid™ system, which takes advantage of transcriptional factors that are composed of two physically separable, functional domains (Chen *et al.*, 1991, *Proc Natl Acad Sci U S A* **88**(21): 9578-9582; Phizicky and Fields, 1994, *Microbiol. Rev.* **59**(1): 94-123). The most commonly used transcriptional factor used in this system is the yeast GAL4 transcriptional activator consisting of a DNA binding domain and a transcriptional activation domain. Vectors are constructed to encode two hybrid proteins. One hybrid consists of the DNA-binding domain of the yeast transcriptional activator protein GAL4 fused to a known protein; the other hybrid consists of the GAL4 activation domain fused to protein sequences encoded by an expression library. Thus, two different cloning vectors are used to generate separate fusions of the GAL4 domains to genes encoding potential binding proteins. The fusion proteins are co-expressed, targeted to the nucleus and, if interactions occur, activation of a reporter gene (*e.g.*, *lacZ*) produces a detectable phenotype. In the present case, for example, *S. cerevisiae* is transformed with a vector expressing a fusion protein comprising a target molecule of the invention together with the GAL4 binding domain. The *S. cerevisiae* is co-transformed with a second vector expressing a second fusion protein comprising another protein encoded by a chlamydial expression library together with the GAL4 activation domain. The second vector is suitably constructed using a chlamydial expression library. Such expression libraries may be formed by any suitable technique known to persons of skill in the art. Methods for producing chlamydial expression libraries are described, for example, by Neurath *et al.* (1999, *Biologicals* **27**(1): 11-21), Bannantine *et al.* (1998, *Molecular Microbiology* **28**(5): 1017-1026) Knudsen *et al.* (1999, *Infection & Immunity* **67**(1): 375-383), Pham *et al.* (1998, *Journal of Clinical Microbiology* **36**(7): 1919-1922) and Zhang *et al.* (1997, *Archives of Biochemistry & Biophysics* **344**(1): 43-52). If *lacZ* is used as the reporter gene, co-expression of the fusion proteins will produce a blue colour if there is interaction between the two co-expressed fusion proteins. Chlamydial proteins thus identified by this system could then be tested to determine whether their levels and/or functional activities are altered in the persistent phase of the chlamydial developmental cycle.

The present inventors have found that *pyk*, *nlpD*, *Cpn0585*, *ompA*, *ompB*, *hsp60* are expressed at significantly elevated levels in the persistent state and are, therefore, ideal targets for agents that will abrogate or otherwise reduce the level and/or functional activity of their encoded protein products in the chronically infected host cells, to thereby kill or

otherwise inactivate or attenuate these persistent chlamydial forms or to cause them to revert or enter the lytic phase of the chlamydial developmental cycle. It is possible that such agents would most likely be chlamydial-specific and could, therefore, be used for more extended periods than conventional antibiotics, which might prove more efficacious in eliminating these chronic infections. Accordingly, in one embodiment, the agent reduces the expression of said gene or the level and/or functional activity of said expression product. In a preferred embodiment of this type, the agent reduces, abrogates or otherwise impairs the expression of *pyk*, *nlpD*, *Cpn0585*, *ompA*, *ompB*, *hsp60* or the level and/or functional activity of an expression product of these genes.

Agents that may be used to reduce or abrogate gene expression include, but are not restricted to, oligoribonucleotide sequences, including anti-sense RNA and DNA molecules and ribozymes, that function to inhibit the translation of mRNA relating to one or more of said genes. Anti-sense RNA and DNA molecules act to directly block the translation of mRNA by binding to targeted mRNA and preventing protein translation. In regard to antisense DNA, oligodeoxyribonucleotides derived from the translation initiation site, *e.g.*, between -10 and +10 regions of a target gene, are preferred.

Ribozymes are enzymatic RNA molecules capable of catalysing the specific cleavage of RNA. The mechanism of ribozyme action involves sequence specific hybridisation of the ribozyme molecule to complementary target RNA, followed by a endonucleolytic cleavage. Within the scope of the invention are engineered hammerhead motif ribozyme molecules that specifically and efficiently catalyse endonucleolytic cleavage of RNA sequences relating to said target molecules. Specific ribozyme cleavage sites within any potential RNA target are initially identified by scanning the target molecule for ribozyme cleavage sites, which include the following sequences, GUA, GUU and GUC. Once identified, short RNA sequences of between 15 and 20 ribonucleotides corresponding to the region of the target gene containing the cleavage site may be evaluated for predicted structural features such as secondary structure that may render the oligonucleotide sequence unsuitable. The suitability of candidate targets may also be evaluated by testing their accessibility to hybridisation with complementary oligonucleotides, using ribonuclease protection assays.

Both anti-sense RNA and DNA molecules and ribozymes may be prepared by any method known in the art for the synthesis of RNA molecules. These include techniques for chemically synthesising oligodeoxyribonucleotides well known in the art such as for example solid phase phosphoramidite chemical synthesis. Alternatively, RNA molecules may be generated by *in vitro* or *in vivo* transcription of DNA sequences encoding the antisense RNA molecule. Such DNA sequences may be incorporated into a wide variety of vectors that incorporate suitable RNA polymerase promoters such as the T7 or SP6 polymerase promoters. Alternatively, antisense cDNA constructs that synthesise antisense RNA constitutively or inducibly, depending on the promoter used, can be introduced stably into cell lines.

Various modifications to the DNA molecules may be introduced as a means of increasing intracellular stability and half-life. Possible modifications include but are not limited to the addition of flanking sequences of ribo- or deoxy- nucleotides to the 5' and/or 3' ends of the molecule or the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages within the oligodeoxyribonucleotide backbone.

The present invention also contemplates use in the above method of gene or expression product inhibitors identified by a method described for example in Section 3, *infra*.

In another embodiment, the agent increases, enhances or otherwise elevates the expression of said gene or the level and/or functional activity of said expression product. In a preferred embodiment of this type, the agent increases, enhances or otherwise elevates the expression of a gene (*e.g.*, a negative regulator) or the level and/or functional activity of an expression product of said gene, which reduces, abrogates or otherwise impairs the expression of *pyk*, *nlpD*, *Cpn0585*, *ompA*, *ompB* or *hsp60*, or the level and/or functional activity of an expression product of *pyk*, *nlpD*, *Cpn0585*, *ompA*, *ompB* or *hsp60*. Any suitable inducers or stabilising/activating agents may be used in this regard and these can be identified or produced by methods for example disclosed in Section 3 *infra*. Alternatively, such an agent may comprise a polynucleotide, which encodes a negative regulator of one or more of *pyk*, *nlpD*, *Cpn0585*, *ompA*, *ompB* or *hsp60*, or a polypeptide, which reduces, abrogates or otherwise impairs the level and/or functional activity of one or more expression products of these genes.

The modulatory agent of the invention will suitably promote or affect the switching of the species from the persistent phase to the lytic phase or will promote death of the species in the persistent phase. Any suitable assay of the lytic phase is contemplated by the present invention. For example, viable elementary bodies (EBs) may be detected in a cell or tissue sample by culture, which is indicative of a lytic infection. Alternatively, morphology based assays may be employed using, for example, transmission electron microscopy (TEM), direct immunofluorescence antibody staining (DFA) or phase contrast microscopy as is known in the art. EBs are easily distinguished because they are small (200 nm) and spherical, they have an electron dense nucleoid and uniform outer membrane structure by TEM and are substantially spherical with intensely stained outer membrane by DFA. RBs range in size from 500-800 nm and are uniformly spherical with low-density to high-density nucleoid with structured outer membrane by TEM and strong (but not as strong as EB) staining by DFA. Inclusions stained by DFA show high levels of fluorescence in a spherical area where the individual chlamydial particles can be distinguished. In contrast, particles involved in "chronic" infections are typically larger than RBs (800-1500 nm) and usually do no stain as well by DFA. Using TEM, chronic infection related particles have an unstructured outer membrane and the nucleoid appears dispersed compared to the EB and RB. Antigen-binding molecules, preferably monoclonal antibodies that are immuno-interactive with the genus specific-LPS or species specific-MOMP may be employed for DFA. Alternatively, a nucleic acid based assay, preferably reverse transcriptase polymerase chain reaction (RT-PCR), may be used to quantify the level of expression in a biological sample of a gene selected from *pyk*, *nlpD*, *Cpn0585* or a gene belonging to the same regulatory or biosynthetic pathway as *pyk*, *nlpD*, *Cpn0585*, *ompA*, *ompB*, *hsp60* or as a gene involved in the biosynthesis of LPS, or a variant of said gene.

3. *Identification of target molecule modulators*

The invention also features a method of screening for an agent that modulates the expression of a gene selected from *pyk*, *nlpD*, *Cpn0585*, or a gene belonging to the same regulatory or biosynthetic pathway as *pyk*, *nlpD*, *Cpn0585*, *ompA*, *ompB*, *hsp60* or as a gene involved in the biosynthesis of LPS, or a variant of said gene, or the that modulates the level and/or functional activity of an expression product of said gene. The method

comprises contacting a preparation comprising said expression product (*e.g.*, polypeptide or transcript), or a biologically active fragment thereof, or variant or derivative of these, or a genetic sequence that modulates the expression of said gene (*e.g.*, the natural promoter relating to said gene), with a test agent, and detecting a change in the level and/or functional activity of said polypeptide or biologically active fragment thereof, or variant or derivative, or of a product expressed from said genetic sequence.

Modulators contemplated by the present invention includes agonists and antagonists of gene expression include antisense molecules, ribozymes and co-suppression molecules, as for example described in Section 2. Agonists include molecules which increase promoter activity or interfere with negative mechanisms. Agonists of a gene include molecules which overcome any negative regulatory mechanism. Antagonists of polypeptides encoded by a gene of interest include antibodies and inhibitor peptide fragments.

Candidate agents encompass numerous chemical classes, though typically they are organic molecules, preferably small organic compounds having a molecular weight of more than 50 and less than about 2,500 Dalton. Candidate agents comprise functional groups necessary for structural interaction with proteins, particularly hydrogen bonding, and typically include at least an amine, carbonyl, hydroxyl or carboxyl group, preferably at least two of the functional chemical groups. The candidate agents often comprise cyclical carbon or heterocyclic structures and/or aromatic or polyaromatic structures substituted with one or more of the above functional groups. Candidate agents are also found among biomolecules including, but not limited to: peptides, saccharides, fatty acids, steroids, purines, pyrimidines, derivatives, structural analogues or combinations thereof.

Small (non-peptide) molecule modulators of a polypeptide according to the invention (especially Pyk, NlpD and CPn0585) are particularly preferred. In this regard, small molecules are particularly preferred because such molecules are more readily absorbed after oral administration, have fewer potential antigenic determinants, and/or are more likely to cross the cell membrane than larger, protein-based pharmaceuticals. Small organic molecules may also have the ability to gain entry into an appropriate cell and affect the expression of a gene (*e.g.*, by interacting with the regulatory region or

transcription factors involved in gene expression); or affect the activity of a gene by inhibiting or enhancing the binding of accessory molecules.

Alternatively, libraries of natural compounds in the form of bacterial, fungal, plant and animal extracts are available or readily produced. Additionally, natural or synthetically produced libraries and compounds are readily modified through conventional chemical, physical and biochemical means, and may be used to produce combinatorial libraries. Known pharmacological agents may be subjected to directed or random chemical modifications, such as acylation, alkylation, esterification, amidification, etc. to produce structural analogues.

Screening may also be directed to known pharmacologically active compounds and chemical analogues thereof.

Screening for modulatory agents according to the invention can be achieved by any suitable method. For example, the method may include contacting a cell comprising a polynucleotide corresponding to a gene selected from *pyk*, *nlpD*, *Cpn0585* or a gene belonging to the same regulatory or biosynthetic pathway as *pyk*, *nlpD*, *Cpn0585*, *ompA*, *ompB*, *hsp60*, or as a gene involved in the biosynthesis of LPS, or a variant of said gene, with an agent suspected of having said modulatory activity and screening for the modulation of the level and/or functional activity of a protein encoded by said polynucleotide, or the modulation of the level of a transcript encoded by the polynucleotide, or the modulation of the activity or expression of a downstream cellular target of said protein or said transcript. Detecting such modulation can be achieved utilising techniques including, but not restricted to, ELISA, cell-based ELISA, filter-binding ELISA, inhibition ELISA, Western blots, North Western blots, immunoprecipitation, slot or dot blot assays, immunostaining, RIA, scintillation proximity assays, fluorescent immunoassays using antigen-binding molecule conjugates or antigen conjugates of fluorescent substances such as fluorescein or rhodamine, Ouchterlony double diffusion analysis, immunoassays employing an avidin-biotin or a streptavidin-biotin detection system, and nucleic acid detection assays including reverse transcriptase polymerase chain reaction (RT-PCR) and gel retardation assays.

It will be understood that a polynucleotide from which a target molecule of interest is regulated or expressed may be naturally occurring in the cell which is the subject of testing or it may have been introduced into the host cell for the purpose of testing. Further, the naturally-occurring or introduced sequence may be constitutively expressed – thereby providing a model useful in screening for agents which down-regulate expression of an encoded product of the sequence wherein said down regulation can be at the nucleic acid or expression product level – or may require activation – thereby providing a model useful in screening for agents that up-regulate expression of an encoded product of the sequence. Further, to the extent that a polynucleotide is introduced into a cell, that polynucleotide may comprise the entire coding sequence which codes for a target protein or it may comprise a portion of that coding sequence (*e.g.* a domain such as a protein binding domain) or a portion that regulates expression of a product encoded by the polynucleotide (*e.g.*, a promoter). For example, the promoter that is naturally associated with the polynucleotide may be introduced into the cell that is the subject of testing. In this regard, where only the promoter is utilised, detecting modulation of the promoter activity can be achieved, for example, by operably linking the promoter to a suitable reporter polynucleotide including, but not restricted to, green fluorescent protein (GFP), luciferase, β-galactosidase and catecholamine acetyl transferase (CAT). Modulation of expression may be determined by measuring the activity associated with the reporter polynucleotide.

In another example, the subject of detection could be a downstream regulatory target of the target molecule, rather than target molecule itself or the reporter polynucleotide operably linked to a promoter of a gene encoding a product the expression of which is regulated by the target protein.

These methods provide a mechanism for performing high throughput screening of putative modulatory agents such as proteinaceous or non-proteinaceous agents comprising synthetic, combinatorial, chemical and natural libraries. These methods will also facilitate the detection of agents which bind either the polynucleotide encoding the target molecule or which modulate the expression of an upstream molecule, which subsequently modulates the expression of the polynucleotide encoding the target molecule. Accordingly, these methods provide a mechanism of detecting agents that either directly or indirectly modulate the expression and/or activity of a target molecule according to the invention.

In a series of preferred embodiments, the present invention provides assays for identifying small molecules or other compounds (*i.e.*, modulatory agents) which are capable of inducing or inhibiting the level and/or or functional activity of target molecules according to the invention. The assays may be performed *in vitro* using non-transformed cells, immortalised cell lines, or recombinant cell lines. In addition, the assays may detect the presence of increased or decreased expression of genes or production of proteins on the basis of increased or decreased mRNA expression (using, for example, the nucleic acid probes disclosed herein), increased or decreased levels of protein products (using, for example, the antigen binding molecules disclosed herein), or increased or decreased levels of expression of a reporter gene (*e.g.*, GFP, β-galactosidase or luciferase) operatively linked to a target molecule-related gene regulatory region in a recombinant construct.

Thus, for example, one may culture cells which produce a particular target molecule and add to the culture medium one or more test compounds. After allowing a sufficient period of time (*e.g.*, 6-72 hours) for the compound to induce or inhibit the level and/or functional activity of the target molecule, any change in said level from an established baseline may be detected using any of the techniques described above and well known in the art. In particularly preferred embodiments, the cells are epithelial cells. Using the nucleic acid probes and/or antigen-binding molecules disclosed herein, detection of changes in the level and or functional activity of a target molecule, and thus identification of the compound as agonist or antagonist of the target molecule, requires only routine experimentation.

In particularly preferred embodiments, a recombinant assay is employed in which a reporter polynucleotide encoding, for example, GFP, β-galactosidase or luciferase is operably linked to the 5' regulatory regions of a target molecule related gene. Such regulatory regions may be easily isolated and cloned by one of ordinary skill in the art in light of the present disclosure of the coding regions of these genes. The reporter gene and regulatory regions are joined in-frame (or in each of the three possible reading frames) so that transcription and translation of the reporter gene may proceed under the control of the regulatory elements of the target molecule related gene. The recombinant construct may then be introduced into any appropriate cell type although mammalian cells are preferred, and human cells are most preferred. The transformed cells may be grown in culture and,

after establishing the baseline level of expression of the reporter gene, test compounds may be added to the medium. The ease of detection of the expression of the reporter gene provides for a rapid, high throughput assay for the identification of agonists or antagonists of the target molecules of the invention.

Compounds identified by this method will have potential utility in modifying the expression of target molecule related genes *in vivo*. These compounds may be further tested in the animal models to identify those compounds having the most potent *in vivo* effects. In addition, as described above with respect to small molecules having target polypeptide binding activity, these molecules may serve as "lead compounds" for the further development of pharmaceuticals by, for example, subjecting the compounds to sequential modifications, molecular modelling, and other routine procedures employed in rational drug design.

In another embodiment, a target molecule modulator can be identified by measuring the ability of a candidate agent to decrease the number of cells in an animal, which contain the persistent form of a species of a genus belonging to the family Chlamydiaceae. The animal is preferably a mammal such as a rabbit, gerbil, mouse, or rat. In this regard, reference may be made to Yang *et al.* (1993, *Infection and Immunity* **61**: 2037-2040) and Fong *et al.* (1999, *Infection and Immunity* **67**: 6048-6055), who describe a mouse model and a rabbit model, respectively for studying the pathogenesis of *C. pneumoniae*. In one embodiment of this method, a candidate agent is administered to the mammal, and the number of cells containing a said species in the persistent phase is determined using morphology based assays as, for example, described above. A compound tests positive if the number of cells containing persistent form(s) of said species in a sample taken from the animal to which the agent had been administered is less than that present in an equivalent sample from an untreated animal.

In yet another embodiment, random peptide libraries consisting of all possible combinations of amino acids attached to a solid phase support may be used to identify peptides that are able to bind to a target molecule or to a functional domain thereof. Identification of molecules that are able to bind to a target molecule may be accomplished by screening a peptide library with a recombinant soluble target molecule. The target molecule may be purified, recombinantly expressed or synthesised by any suitable

technique. Such molecules may be conveniently prepared by a person skilled in the art using standard protocols as for example described in Sambrook, *et al.*, MOLECULAR CLONING. A LABORATORY MANUAL (Cold Spring Harbor Press, 1989), in particular Sections 16 and 17; Ausubel *et al.*, CURRENT PROTOCOLS IN MOLECULAR BIOLOGY (John Wiley & Sons, Inc. 1994-1998), in particular Chapters 10 and 16; and Coligan *et al.*, CURRENT PROTOCOLS IN PROTEIN SCIENCE (John Wiley & Sons, Inc. 1995-1997), in particular Chapters 1, 5 and 6. Alternatively, a target polypeptide according to the invention may be synthesised using solution synthesis or solid phase synthesis as described, for example, in Chapter 9 of Atherton and Shephard (*supra*) and in Roberge *et al* (1995, *Science* **269**: 202).

To identify and isolate the peptide/solid phase support that interacts and forms a complex with a target molecule, preferably a target polypeptide, it is necessary to label or "tag" the target polypeptide. The target polypeptide may be conjugated to any suitable reporter molecule, including enzymes such as alkaline phosphatase and horseradish peroxidase and fluorescent reporter molecules such as fluorescein isothyiocynate (FITC), phycoerythrin (PE) and rhodamine. Conjugation of any given reporter molecule, with target polypeptide, may be performed using techniques that are routine in the art. Alternatively, target polypeptide expression vectors may be engineered to express a chimeric target polypeptide containing an epitope for which a commercially available antigen-binding molecule exists. The epitope specific antigen-binding molecule may be tagged using methods well known in the art including labelling with enzymes, fluorescent dyes or coloured or magnetic beads.

For example, the "tagged" target polypeptide conjugate is incubated with the random peptide library for 30 minutes to one hour at 22° C to allow complex formation between target polypeptide and peptide species within the library. The library is then washed to remove any unbound target polypeptide. If the target polypeptide has been conjugated to alkaline phosphatase or horseradish peroxidase the whole library is poured into a petri dish containing a substrate for either alkaline phosphatase or peroxidase, for example, 5-bromo-4-chloro-3-indoyl phosphate (BCIP) or 3,3',4,4"-diamnobenzidine (DAB), respectively. After incubating for several minutes, the peptide/solid phase-target polypeptide complex changes colour, and can be easily identified and isolated physically

under a dissecting microscope with a micromanipulator. If a fluorescently tagged target polypeptide has been used, complexes may be isolated by fluorescent activated sorting. If a chimeric target polypeptide having a heterologous epitope has been used, detection of the peptide/target polypeptide complex may be accomplished by using a labelled epitope specific antigen-binding molecule. Once isolated, the identity of the peptide attached to the solid phase support may be determined by peptide sequencing.

4. Variant polypeptides

The invention also contemplates the use and detection of variants of the polypeptide products of *pyk*, *nlpD*, *Cpn0585*, or of a gene belonging to the same regulatory or biosynthetic pathway as *pyk*, *nlpD*, *Cpn0585*, *ompA*, *ompB*, *hsp60* or as a gene involved in the biosynthesis of LPS, wherein the variants comprise an activity of a reference polypeptide of the invention. Variant or homologous polypeptides corresponding to other chlamydial isolates are known and it will be understood that such variant polypeptides are also encompassed by the present invention. Alternatively, variant polypeptides may be deduced from other species belonging to the family Chlamydiaceae by isolation of polynucleotide variants by standard protocols known in the art. In general, variants will be at least 50%, preferably at least 55%, more preferably at least 60%, even more preferably at least 65%, even more preferably at least 70%, even more preferably at least 75%, even more preferably at least 80%, even more preferably at least 85%, even more preferably at least 90% and still even more preferably at least 95% homologous to a polypeptide as for example shown in any one of SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34 or 36, or in fragments thereof. Suitably, variants will have at least 50%, preferably at least 55%, more preferably at least 60%, even more preferably at least 65%, even more preferably at least 70%, even more preferably at least 75%, even more preferably at least 80%, even more preferably at least 85%, even more preferably at least 90% and still even more preferably at least 95% sequence identity to the sequence set forth in any one of SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34 or 36.

Variant peptides or polypeptides, resulting from rational or established methods of mutagenesis or from combinatorial chemistries, for example, may comprise conservative amino acid substitutions. Exemplary conservative substitutions in a polypeptide or

polypeptide fragment according to the invention may be made according to TABLE B, *supra*.

5. ***Polypeptide derivatives***

With reference to suitable derivatives of the invention, such derivatives include amino acid deletions and/or additions to a polypeptide, fragment or variant of the invention, wherein said derivatives comprise an activity of a reference polypeptide of the invention (*e.g.*, pyruvate kinase activity, inclusion membrane protein function). *"Additions"* of amino acids may include fusion of the polypeptides, fragments and polypeptide variants of the invention with other polypeptides or proteins. For example, it will be appreciated that said polypeptides, fragments or variants may be incorporated into larger polypeptides, and that such larger polypeptides may also be expected to have an activity of the parent polypeptide.

The polypeptides, fragments or variants of the invention may be fused to a further protein, for example, which is not derived from the original host. The further protein may assist in the purification of the fusion protein. For instance, a polyhistidine tag or a maltose binding protein may be used in this respect as described in more detail below. Other possible fusion proteins are those which produce an immunomodulatory response. Particular examples of such proteins include Protein A or glutathione S-transferase (GST).

Other derivatives contemplated by the invention include, but are not limited to, modification to side chains, incorporation of unnatural amino acids and/or their derivatives during peptide, polypeptide or protein synthesis and the use of crosslinkers and other methods which impose conformational constraints on the polypeptides, fragments and variants of the invention. Examples of side chain modifications contemplated by the present invention include modifications of amino groups such as by acylation with acetic anhydride; acylation of amino groups with succinic anhydride and tetrahydrophthalic anhydride; amidination with methylacetimidate; carbamoylation of amino groups with cyanate; pyridoxylation of lysine with pyridoxal-5-phosphate followed by reduction with $NaBH_4$; reductive alkylation by reaction with an aldehyde followed by reduction with $NaBH_4$; and trinitrobenzylation of amino groups with 2, 4, 6-trinitrobenzene sulphonic acid (TNBS). The carboxyl group may be modified by carbodiimide activation via O-

acylisourea formation followed by subsequent derivatisation, by way of example, to a corresponding amide. The guanidine group of arginine residues may be modified by formation of heterocyclic condensation products with reagents such as 2,3-butanedione, phenylglyoxal and glyoxal. Sulphydryl groups may be modified by methods such as performic acid oxidation to cysteic acid; formation of mercurial derivatives using 4-chloromercuriphenylsulphonic acid, 4-chloromercuribenzoate; 2-chloromercuri-4-nitrophenol, phenylmercury chloride, and other mercurials; formation of a mixed disulphides with other thiol compounds; reaction with maleimide, maleic anhydride or other substituted maleimide; carboxymethylation with iodoacetic acid or iodoacetamide; and carbamoylation with cyanate at alkaline pH. Tryptophan residues may be modified, for example, by alkylation of the indole ring with 2-hydroxy-5-nitrobenzyl bromide or sulphonyl halides or by oxidation with N-bromosuccinimide. Tyrosine residues may be modified by nitration with tetranitromethane to form a 3-nitrotyrosine derivative. The imidazole ring of a histidine residue may be modified by N-carbethoxylation with diethylpyrocarbonate or by alkylation with iodoacetic acid derivatives.

Examples of incorporating unnatural amino acids and derivatives during peptide synthesis include but are not limited to, use of 4-amino butyric acid, 6-aminohexanoic acid, 4-amino-3-hydroxy-5-phenylpentanoic acid, 4-amino-3-hydroxy-6-methylheptanoic acid, t-butylglycine, norleucine, norvaline, phenylglycine, ornithine, sarcosine, 2-thienyl alanine and/or D-isomers of amino acids.

The invention also contemplates polypeptides, fragments or variants of the invention that have been modified using ordinary molecular biological techniques so as to improve their resistance to proteolytic degradation or to optimise solubility properties or to render them more suitable as an immunogenic agent.

6. *Methods of preparing a polypeptide of the invention*

A polypeptide of the invention, or fragment thereof, or variant or derivative of these, may be prepared by any suitable procedure known to those of skill in the art. For example, a polypeptide may be prepared by a procedure including the steps of (a) preparing a recombinant polynucleotide comprising a nucleotide sequence encoding a polypeptide comprising the sequence set forth in any one of SEQ ID NO: 2, 4, 6, 8, 10, 12,

14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34 or 36, or a biologically active fragment thereof, or variant or derivative of these, which nucleotide sequence is operably linked to regulatory elements; (b) introducing the recombinant polynucleotide into a suitable host cell; (c) culturing the host cell to express recombinant polypeptide from said recombinant polynucleotide; and (d) isolating the recombinant polypeptide. Preferred nucleotide sequences include, but are not limited to the sequences set forth in SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33 or 35.

The recombinant polynucleotide is preferably in the form of an expression vector that may be a self-replicating extra-chromosomal vector such as a plasmid, or a vector that integrates into a host genome. The regulatory elements will generally be appropriate for the host cell used for expression. Numerous types of appropriate expression vectors and suitable regulatory sequences are known in the art for a variety of host cells. Typically, the regulatory elements include, but are not limited to, promoter sequences, leader or signal sequences, ribosomal binding sites, transcriptional start and stop sequences, translational start and termination sequences, and enhancer or activator sequences. Constitutive or inducible promoters as known in the art are contemplated by the invention. The promoters may be either naturally occurring promoters, or hybrid promoters that combine elements of more than one promoter.

In a preferred embodiment, the expression vector contains a selectable marker gene to allow the selection of transformed host cells. Selection genes are well known in the art and will vary with the host cell used.

The expression vector may also include a fusion partner (typically provided by the expression vector) so that the recombinant polypeptide of the invention is expressed as a fusion polypeptide with said fusion partner. The main advantage of fusion partners is that they assist identification and/or purification of said fusion polypeptide. In order to express said fusion polypeptide, it is necessary to ligate a polynucleotide according to the invention into the expression vector so that the translational reading frames of the fusion partner and the polynucleotide coincide. Well known examples of fusion partners include, but are not limited to, glutathione-S-transferase (GST), Fc potion of human IgG, maltose binding protein (MBP) and hexahistidine (HIS_6), which are particularly useful for isolation of the fusion polypeptide by affinity chromatography. For the purposes of fusion polypeptide

purification by affinity chromatography, relevant matrices for affinity chromatography are glutathione-, amylose-, and nickel- or cobalt-conjugated resins respectively. Many such matrices are available in "kit" form, such as the QIAexpress™ system (Qiagen) useful with (HIS_6) fusion partners and the Pharmacia GST purification system. In a preferred embodiment, the recombinant polynucleotide is expressed in the commercial vector pFLAG as described more fully hereinafter. Another fusion partner well known in the art is green fluorescent protein (GFP). This fusion partner serves as a fluorescent "tag" which allows the fusion polypeptide of the invention to be identified by fluorescence microscopy or by flow cytometry. The GFP tag is useful when assessing subcellular localisation of the fusion polypeptide of the invention, or for isolating cells which express the fusion polypeptide of the invention. Flow cytometric methods such as fluorescence activated cell sorting (FACS) are particularly useful in this latter application. Preferably, the fusion partners also have protease cleavage sites, such as for Factor X_a or Thrombin, which allow the relevant protease to partially digest the fusion polypeptide of the invention and thereby liberate the recombinant polypeptide of the invention therefrom. The liberated polypeptide can then be isolated from the fusion partner by subsequent chromatographic separation. Fusion partners according to the invention also include within their scope "epitope tags", which are usually short peptide sequences for which a specific antibody is available. Well known examples of epitope tags for which specific monoclonal antibodies are readily available include c-Myc, influenza virus, haemagglutinin and FLAG tags. In an especially preferred embodiment, the vector is pPROEx (Life Technologies).

The step of introducing into the host cell the recombinant polynucleotide may be effected by any suitable method including transfection, and transformation, the choice of which will be dependent on the host cell employed. Such methods are well known to those of skill in the art.

Recombinant polypeptides of the invention may be produced by culturing a host cell transformed with an expression vector containing nucleic acid encoding a polypeptide, biologically active fragment, variant or derivative according to the invention. The conditions appropriate for protein expression will vary with the choice of expression vector and the host cell. This is easily ascertained by one skilled in the art through routine experimentation.

Suitable host cells for expression may be prokaryotic or eukaryotic. One preferred host cell for expression of a polypeptide according to the invention is a bacterium. The bacterium used may be *Escherichia coli*. Alternatively, the host cell may be an insect cell such as, for example, *SF9* cells that may be utilised with a baculovirus expression system.

The recombinant protein may be conveniently prepared by a person skilled in the art using standard protocols as for example described in Sambrook, *et al.*, 1989, in particular Sections 16 and 17; Ausubel *et al.*, (1994-1998), in particular Chapters 10 and 16; and Coligan *et al.*, (1995-1997), in particular Chapters 1, 5 and 6. Alternatively, the polypeptide, fragment, variant or derivative may be synthesised using solution synthesis or solid phase synthesis as described, for example, in Chapter 9 of Atherton and Shephard (*supra*) and in Roberge *et al* (1995).

7. Polynucleotides variants

In general, polynucleotide variants according to the invention comprise regions that show at least 50%, preferably at least 55%, more preferably at least 60%, even more preferably at least 65%, even more preferably at least 70%, even more preferably at least 75%, even more preferably at least 80%, even more preferably at least 85%, even more preferably at least 90% and still even more preferably at least 95% sequence identity over a reference polynucleotide sequence of identical size ("*comparison window*") or when compared to an aligned sequence in which the alignment is performed by a computer homology program known in the art. In accordance with the present invention, the reference polynucleotide sequence corresponds to a gene selected from *pyk*, *nlpD*, *Cpn0585*, or a gene belonging to the same regulatory or biosynthetic pathway as *pyk*, *nlpD*, *Cpn0585*, *ompA*, *ompB*, *hsp60* or as a gene involved in the biosynthesis of LPS.

What constitutes suitable variants may be determined by conventional techniques. For example, a polynucleotide according to any one of SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33 or 35 can be mutated using random mutagenesis (*e.g.*, transposon mutagenesis), oligonucleotide-mediated (or site-directed) mutagenesis, PCR mutagenesis and cassette mutagenesis as is known in the art.

blotting and slot blotting, DNA samples are directly applied to a synthetic membrane prior to hybridisation as above.

An alternative blotting step is used when identifying complementary polynucleotides in a cDNA or genomic DNA library, such as through the process of plaque or colony hybridisation. A typical example of this procedure is described in Sambrook *et al.* (1989) Chapters 8-12.

Typically, the following general procedure can be used to determine hybridisation conditions. Polynucleotides are blotted/transferred to a synthetic membrane, as described above. A reference polynucleotide such as a polynucleotide of the invention is labelled as described above, and the ability of this labelled polynucleotide to hybridise with an immobilised polynucleotide is analysed.

A skilled artisan will recognise that a number of factors influence hybridisation. The specific activity of radioactively labelled polynucleotide sequence should typically be greater than or equal to about 10^8 dpm/mg to provide a detectable signal. A radiolabelled nucleotide sequence of specific activity 10^8 to 10^9 dpm/mg can detect approximately 0.5 pg of DNA. It is well known in the art that sufficient DNA must be immobilised on the membrane to permit detection. It is desirable to have excess immobilised DNA, usually 10 µg. Adding an inert polymer such as 10% (w/v) dextran sulphate (MW 500,000) or polyethylene glycol 6000 during hybridisation can also increase the sensitivity of hybridisation (see Ausubel *supra* at 2.10.10).

To achieve meaningful results from hybridisation between a polynucleotide immobilised on a membrane and a labelled polynucleotide, a sufficient amount of the labelled polynucleotide must be hybridised to the immobilised polynucleotide following washing. Washing ensures that the labelled polynucleotide is hybridised only to the immobilised polynucleotide with a desired degree of complementarity to the labelled polynucleotide.

It will be understood that polynucleotide variants according to the invention will hybridise to a reference polynucleotide under at least low stringency conditions. Reference herein to low stringency conditions include and encompass from at least about 1% v/v to at

Alternatively, suitable polynucleotide sequence variants of the invention may be prepared according to the following procedure: creating primers which are optionally degenerate wherein each comprises a portion of a reference polynucleotide encoding a reference polypeptide or fragment of the invention, preferably encoding the sequence set forth in SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34 or 36; obtaining a nucleic acid extract from an organism, which is preferably an animal, and more preferably a mammal; and using said primers to amplify, via nucleic acid amplification techniques, at least one amplification product from said nucleic acid extract, wherein said amplification product corresponds to a polynucleotide variant.

Suitable nucleic acid amplification techniques are well known to the skilled artisan, and include polymerase chain reaction (PCR) as for example described in Ausubel *et al.* (*supra*); strand displacement amplification (SDA) as for example described in U.S. Patent No 5,422,252; rolling circle replication (RCR) as for example described in Liu *et al.*, (1996) and International application WO 92/01813) and Lizardi *et al.*, (International Application WO 97/19193); nucleic acid sequence-based amplification (NASBA) as for example described by Sooknanan *et al.*, (1994); and Q-β replicase amplification as for example described by Tyagi *et al.*, (1996).

Typically, polynucleotide variants that are substantially complementary to a reference polynucleotide are identified by blotting techniques that include a step whereby nucleic acids are immobilised on a matrix (preferably a synthetic membrane such as nitrocellulose), followed by a hybridisation step, and a detection step. Southern blotting is used to identify a complementary DNA sequence; northern blotting is used to identify a complementary RNA sequence. Dot blotting and slot blotting can be used to identify complementary DNA/DNA, DNA/RNA or RNA/RNA polynucleotide sequences. Such techniques are well known by those skilled in the art, and have been described in Ausubel *et al.* (1994-1998, *supra*) at pages 2.9.1 through 2.9.20.

According to such methods, Southern blotting involves separating DNA molecules according to size by gel electrophoresis, transferring the size-separated DNA to a synthetic membrane, and hybridising the membrane-bound DNA to a complementary nucleotide sequence labelled radioactively, enzymatically or fluorochromatically. In dot

least about 15% v/v formamide and from at least about 1 M to at least about 2 M salt for hybridisation at 42° C, and at least about 1 M to at least about 2 M salt for washing at 42° C. Low stringency conditions also may include 1% Bovine Serum Albumin (BSA), 1 mM EDTA, 0.5 M $NaHPO_4$ (pH 7.2), 7% SDS for hybridisation at 65° C, and (i) 2xSSC, 0.1% SDS; or (ii) 0.5% BSA, 1 mM EDTA, 40 mM $NaHPO_4$ (pH 7.2), 5% SDS for washing at room temperature.

Suitably, the polynucleotide variants hybridise to a reference polynucleotide under at least medium stringency conditions. Medium stringency conditions include and encompass from at least about 16% v/v to at least about 30% v/v formamide and from at least about 0.5 M to at least about 0.9 M salt for hybridisation at 42° C, and at least about 0.1 M to at least about 0.2 M salt for washing at 55° C. Medium stringency conditions also may include 1% Bovine Serum Albumin (BSA), 1 mM EDTA, 0.5 M $NaHPO_4$ (pH 7.2), 7% SDS for hybridisation at 65° C, and (i) 2 x SSC, 0.1% SDS; or (ii) 0.5% BSA, 1 mM EDTA, 40 mM $NaHPO_4$ (pH 7.2), 5% SDS for washing at 60-65° C.

Preferably, the polynucleotide variants hybridise to a reference polynucleotide under high stringency conditions. High stringency conditions include and encompass from at least about 31% v/v to at least about 50% v/v formamide and from about 0.01 M to about 0.15 M salt for hybridisation at 42° C, and about 0.01 M to about 0.02 M salt for washing at 55° C. High stringency conditions also may include 1% BSA, 1 mM EDTA, 0.5 M $NaHPO_4$ (pH 7.2), 7% SDS for hybridisation at 65° C, and (i) 0.2 x SSC, 0.1% SDS; or (ii) 0.5% BSA, 1mM EDTA, 40 mM $NaHPO_4$ (pH 7.2), 1% SDS for washing at a temperature in excess of 65° C.

Other stringent conditions are well known in the art. A skilled addressee will recognise that various factors can be manipulated to optimise the specificity of the hybridisation. Optimisation of the stringency of the final washes can serve to ensure a high degree of hybridisation. For detailed examples, see Ausubel *et al.*, *supra* at pages 2.10.1 to 2.10.16 and Sambrook *et al.* (1989, *supra*) at sections 1.101 to 1.104.

While stringent washes are typically carried out at temperatures from about 42° C to 68° C, one skilled in the art will appreciate that other temperatures may be suitable for stringent conditions. Maximum hybridisation rate typically occurs at about 20° C to 25° C

below the T_m for formation of a DNA-DNA hybrid. It is well known in the art that the T_m is the melting temperature, or temperature at which two complementary polynucleotide sequences dissociate. Methods for estimating T_m are well known in the art (see Ausubel *et al.*, *supra* at page 2.10.8).

In general, the T_m of a perfectly matched duplex of DNA may be predicted as an approximation by the formula:

$$T_m = 81.5 + 16.6 (\log_{10} M) + 0.41 (\%G+C) - 0.63 (\% \text{ formamide}) - (600/\text{length})$$

wherein: M is the concentration of Na^+, preferably in the range of 0.01 molar to 0.4 molar; %G+C is the sum of guanosine and cytosine bases as a percentage of the total number of bases, within the range between 30% and 75% G+C; % formamide is the percent formamide concentration by volume; length is the number of base pairs in the DNA duplex.

The T_m of a duplex DNA decreases by approximately 1° C with every increase of 1% in the number of randomly mismatched base pairs. Washing is generally carried out at T_m – 15° C for high stringency, or T_m – 30° C for moderate stringency.

In a preferred hybridisation procedure, a membrane (*e.g.*, a nitrocellulose membrane or a nylon membrane) containing immobilised DNA is hybridised overnight at 42° C in a hybridisation buffer (50% deionised formamide, 5xSSC, 5x Denhardt's solution (0.1% ficoll, 0.1% polyvinylpyrollidone and 0.1% bovine serum albumin), 0.1% SDS and 200 mg/mL denatured salmon sperm DNA) containing labelled probe. The membrane is then subjected to two sequential medium stringency washes (*i.e.*, 2xSSC, 0.1% SDS for 15 min at 45° C, followed by 2xSSC, 0.1% SDS for 15 min at 50° C), followed by two sequential higher stringency washes (*i.e.*, 0.2xSSC, 0.1% SDS for 12 min at 55° C followed by 0.2xSSC and 0.1%SDS solution for 12 min at 65-68° C.

Methods for detecting a labelled polynucleotide hybridised to an immobilised polynucleotide are well known to practitioners in the art. Such methods include autoradiography, phosphorimaging, and chemiluminescent, fluorescent and colorimetric detection.

8. *Detection of the persistent phase of the chlamydial developmental cycle and diagnosis of chronic chlamydial infections*

The invention also features a method for detecting a species of a genus belonging to the family Chlamydiaceae in the persistent phase of its developmental cycle. The method comprises detecting, relative to the lytic phase of said developmental cycle, a change in the level and/or functional activity of an expression product of a gene selected from *pyk, nlpD, Cpn0585*, or a gene belonging to the same regulatory or biosynthetic pathway as *pyk, nlpD, Cpn0585, ompA, ompB, hsp60* or as a gene involved in the biosynthesis of LPS, or a variant of said gene. In a preferred embodiment, the gene is selected from *pyk, nlpD, Cpn0585* or a gene belonging to the same regulatory or biosynthetic pathway as *pyk, nlpD* or *Cpn0585*, or a variant of said gene.

The invention also encompasses a method for diagnosis of a persistent or chronic chlamydial infection in a patient by detecting in a biological sample obtained from said patient a change in the level and/or functional activity of a gene or expression product as described above. Conditions in which it would be particularly important to be able to diagnose persistent chlamydial infection include, but are not restricted to, cardiovascular diseases such as coronary artery disease, carotid artery disease, stroke, aneurisms; chronic respiratory diseases such as chronic obstructive pulmonary disease; chronic infertility problems in females such as tubal blockage); chronic eye infections (such as trachoma). Being able to diagnose the chronic state of chlamydial disease might enable alternate therapy directed at eliminating the persistent state of the chlamydial infection as, for example, described herein.

8.1 Nucleic acid-based detection

One embodiment of the instant invention comprises a method for detecting the persistent phase or for diagnosis of a chronic chlamydial infection comprises qualitatively or quantitatively determining the level of transcript expressed by a gene selected from *pyk, nlpD, Cpn0585*, or a gene belonging to the same regulatory or biosynthetic pathway as *pyk, nlpD, Cpn0585, ompA, ompB, hsp60* or as a gene involved in the biosynthesis of LPS, or a variant of said gene. In a preferred embodiment, the level of said transcript is compared to a reference or baseline level of said transcript corresponding to the lytic phase

of a chlamydial species. In these embodiments, nucleic acid can be isolated from cells contained in the biological sample, according to standard methodologies (Sambrook, *et al.*, "Molecular Cloning. A Laboratory Manual", Cold Spring Harbor Press, 1989; Ausubel *et al.*, "Current Protocols in Molecular Biology", John Wiley & Sons Inc, 1994-1998). The nucleic acid may be genomic DNA or fractionated or whole cell RNA. Where RNA is used, it may be desired to convert the RNA to a complementary DNA. The cell is preferably an epithelial cell including, but not limited to, an epithelial cell of the genital tract, respiratory tract, cardiovascular system, reproductive system (*e.g.*, fallopian tubes) or conjunctiva or from arthritic joints. In one embodiment, the RNA is whole cell RNA; in another, it is poly-A RNA. In one embodiment, the nucleic acid is amplified by a nucleic acid amplification technique. Suitable nucleic acid amplification techniques are well known to the skilled person, and include the polymerase chain reaction (PCR) as for example described in Ausubel *et al.* (*supra*); strand displacement amplification (SDA) as for example described in U.S. Patent No 5,422,252; rolling circle replication (RCR) as for example described in Liu *et al.*, (1996) and International application WO 92/01813) and Lizardi *et al.*, (International Application WO 97/19193); nucleic acid sequence-based amplification (NASBA) as for example described by Sooknanan *et al.*, (1994, *Biotechniques* **17**:1077-1080); and Q-β replicase amplification as for example described by Tyagi *et al.*, (1996, *Proc. Natl. Acad. Sci. USA* **93**: 5395-5400).

Depending on the format, the specific nucleic acid of interest is identified in the sample directly using amplification or with a second, known nucleic acid following amplification. Next, the identified product is detected. In certain applications, the detection may be performed by visual means (*e.g.*, ethidium bromide staining of a gel). Alternatively, the detection may involve indirect identification of the product via chemiluminescence, radioactive scintigraphy of radiolabel or fluorescent label or even via a system using electrical or thermal impulse signals (Affymax Technology; Bellus, 1994, *J Macromol. Sci. Pure, Appl. Chem.*, **A31**(1): 1355-1376).

Following detection, one may compare the results seen in a test sample with a control reaction corresponding to the lytic phase of the developmental cycle of a chlamydial species.

8.2 Protein-based detection

8.2.1 Antigen-binding molecules

Antigen-binding molecules that are immuno-interactive with a target molecule of the present invention can be used in measuring an increase or decrease in the expression of a gene selected from *pyk*, *nlpD*, *Cpn0585*, or a gene belonging to the same regulatory or biosynthetic pathway as *pyk*, *nlpD*, *Cpn0585*, *ompA*, *ompB*, *hsp60* or as a gene involved in the biosynthesis of LPS, or a variant of said gene. Thus, the present invention also contemplates antigen-binding molecules that bind specifically to a polypeptide encoded by those genes or to proteins that regulate or otherwise influence the level and/or functional activity of one or more said polypeptides. For example, the antigen-binding molecules may comprise whole polyclonal antibodies. Such antibodies may be prepared, for example, by injecting a target molecule (*e.g.*, a persistent phase-associated polypeptide or portion thereof, or a lytic phase-associated polypeptide or portion thereof) of the invention into a production species, which may include mice or rabbits, to obtain polyclonal antisera. Methods of producing polyclonal antibodies are well known to those skilled in the art. Exemplary protocols which may be used are described for example in Coligan *et al.*, "Current Protocols In Immunology", (John Wiley & Sons, Inc, 1991), and Ausubel *et al.*, (1994-1998, *supra*), in particular Section III of Chapter 11.

In lieu of the polyclonal antisera obtained in the production species, monoclonal antibodies may be produced using the standard method as described, for example, by Köhler and Milstein (1975, *Nature* **256**, 495-497), or by more recent modifications thereof as described, for example, in Coligan *et al.*, (1991, *supra*) by immortalising spleen or other antibody-producing cells derived from a production species which has been inoculated with target molecule of the invention.

The invention also contemplates as antigen-binding molecules Fv, Fab, Fab' and $F(ab')_2$ immunoglobulin fragments. Alternatively, the antigen-binding molecule may comprise a synthetic stabilised Fv fragment. Exemplary fragments of this type include single chain Fv fragments (sFv, frequently termed scFv) in which a peptide linker is used to bridge the N terminus or C terminus of a V_H domain with the C terminus or N-terminus, respectively, of a V_L domain. ScFv lack all constant parts of whole antibodies and are not

able to activate complement. Suitable peptide linkers for joining the V_H and V_L domains are those which allow the V_H and V_L domains to fold into a single polypeptide chain having an antigen binding site with a three dimensional structure similar to that of the antigen binding site of a whole antibody from which the Fv fragment is derived. Linkers having the desired properties may be obtained by the method disclosed in U.S. Patent No 4,946,778. However, in some cases a linker is absent. ScFvs may be prepared, for example, in accordance with methods outlined in Kreber *et al* (Kreber *et al.* 1997, *J. Immunol. Methods*; **201**(1): 35-55). Alternatively, they may be prepared by methods described in U.S. Patent No 5,091,513, European Patent No 239,400 or the articles by Winter and Milstein (1991, *Nature* **349**:293) and Plünckthun *et al* (1996, In *Antibody engineering: A practical approach.* 203-252).

Alternatively, the synthetic stabilised Fv fragment comprises a disulphide stabilised Fv (dsFv) in which cysteine residues are introduced into the V_H and V_L domains such that in the fully folded Fv molecule the two residues will form a disulphide bond therebetween. Suitable methods of producing dsFv are described for example in (Glockscuther *et al. Biochem.* **29**: 1363-1367; Reiter *et al.* 1994, *J. Biol. Chem.* **269**: 18327-18331; Reiter *et al.* 1994, *Biochem. 33*: 5451-5459; Reiter *et al.* 1994. *Cancer Res.* **54**: 2714-2718; Webber *et al.* 1995, *Mol. Immunol.* **32**: 249-258).

Also contemplated as antigen-binding molecules are single variable region domains (termed dAbs) as for example disclosed in (Ward *et al.* 1989, *Nature* **341**: 544-546; Hamers-Casterman *et al.* 1993, *Nature.* **363**: 446-448; Davies & Riechmann, 1994, *FEBS Lett.* **339**: 285-290).

Alternatively, the antigen-binding molecule may comprise a "minibody". In this regard, minibodies are small versions of whole antibodies, which encode in a single chain the essential elements of a whole antibody. Suitably, the minibody is comprised of the V_H and V_L domains of a native antibody fused to the hinge region and CH3 domain of the immunoglobulin molecule as, for example, disclosed in U.S. Patent No 5,837,821.

In an alternate embodiment, the antigen binding molecule may comprise non-immunoglobulin derived, protein frameworks. For example, reference may be made to (Ku & Schultz, 1995, *Proc. Natl. Acad. Sci. USA*, **92**: 652-6556) which discloses a four-helix

bundle protein cytochrome b562 having two loops randomised to create complementarity determining regions (CDRs), which have been selected for antigen binding.

The antigen-binding molecule may be multivalent (*ie.* having more than one antigen-binding site). Such multivalent molecules may be specific for one or more antigens. Multivalent molecules of this type may be prepared by dimerisation of two antibody fragments through a cysteinyl-containing peptide as, for example disclosed by (Adams *et al.*, 1993, *Cancer Res.* **53**: 4026-4034; Cumber *et al.*, 1992, *J. Immunol.* **149**: 120-126). Alternatively, dimerisation may be facilitated by fusion of the antibody fragments to amphiphilic helices that naturally dimerise (Pack P. Plünckthun, 1992, *Biochem.* **31**: 1579-1584), or by use of domains (such as the leucine zippers jun and fos) that preferentially heterodimerise (Kostelny *et al.*, 1992, *J. Immunol.* **148**: 1547-1553). In an alternate embodiment, the multivalent molecule may comprise a multivalent single chain antibody (multi-scFv) comprising at least two scFvs linked together by a peptide linker. In this regard, non-covalently or covalently linked scFv dimers termed "diabodies" may be used. Multi-scFvs may be bispecific or greater depending on the number of scFvs employed having different antigen binding specificities. Multi-scFvs may be prepared for example by methods disclosed in U.S. Patent No. 5,892,020.

Also contemplated as antigen binding molecules are humanised antibodies. Humanised antibodies are produced by transferring complementary determining regions from heavy and light variable chains of a non human (*e.g.*, rodent, preferably mouse) immunoglobulin into a human variable domain. Typical residues of human antibodies are then substituted in the framework regions of the non human counterparts. The use of antibody components derived from humanised antibodies obviates potential problems associated with the immunogenicity of non human constant regions. General techniques for cloning non human, particular murine, immunoglobulin variable domains are described, for example, by Orlandi *et al.* (1989, *Proc. Natl. Acad. Sci. USA* **86**: 3833). Techniques for producing humanised monoclonal antibodies are described, for example, by Jones *et al.* (1986, *Nature* **321**:522), Carter *et al.* (1992, *Proc. Natl. Acad. Sci. USA* **89**: 4285), Sandhu (1992, *Crit. Rev. Biotech.* **12**: 437), Singer *et al.* (1993, *J. Immun.* **150**: 2844), Sudhir (ed., *Antibody Engineering Protocols*, Humana Press, Inc. 1995), Kelley ("Engineering Therapeutic Antibodies", in *Protein Engineering: Principles and Practice*

Cleland *et al.* (eds.), pages 399-434 (John Wiley & Sons, Inc. 1996), and by Queen *et al.*, U.S. Pat. No. 5,693,762 (1997).

The antigen-binding molecules of the invention may be used for affinity chromatography in isolating a natural or recombinant polypeptide or biologically active fragment of the invention. For example reference may be made to immunoaffinity chromatographic procedures described in Chapter 9.5 of Coligan *et al.*, (1995-1997, *supra*). The antigen-binding molecules can also be used to screen expression libraries for variant polypeptides of the invention as described herein. They can also be used to detect polypeptides, polypeptide fragments, variants and derivatives of the invention.

8.2.2 Immunodiagnostic assays

The above antigen-binding molecules have utility in measuring directly or indirectly modulation of expression of a gene selected from *pyk*, *nlpD*, *Cpn0585*, or of a gene belonging to the same regulatory or biosynthetic pathway as *pyk*, *nlpD*, *Cpn0585*, *ompA*, *ompB*, *hsp60* or as a gene involved in the biosynthesis of LPS, or of a variant of said gene, through techniques such as ELISAs and Western blotting. Illustrative assay strategies which can be used to detect a target polypeptide of the invention include, but are not limited to, immunoassays involving the binding of an antigen-binding molecule to the target polypeptide (*e.g.*, NlpD or Pyk) in the sample, and the detection of a complex comprising the antigen-binding molecule and the target polypeptide. Preferred immunoassays are those that can measure the level and/or functional activity of a target molecule of the invention. Typically, an antigen-binding molecule that is immuno-interactive with a target polypeptide of the invention is contacted with a biological sample suspected of containing said target polypeptide. The biological sample is suitably a specimen, which is suspected of containing a chlamydial organism in its persistent phase. For example, the biological sample may comprise sputums from chronic obstructive pulmonary diseases (COPD) patients, plaque from cardiovascular disease patients or fallopian tube washings from infertile women. The concentration of a complex comprising the antigen-binding molecule and the target polypeptide is measured and the measured complex concentration is then related to the concentration of target polypeptide in the sample. Consistent with the present invention, the concentration of said polypeptide is

compared to a reference or baseline level of said polypeptide corresponding to the lytic phase of the developmental cycle of a chlamydial species under test. The presence of the persistent phase is detected or a chronic chlamydial infection is diagnosed if the concentration of the polypeptide corresponds to a non-reference level concentration.

Any suitable technique for determining formation of an antigen-binding molecule-target antigen complex may be used. For example, an antigen-binding molecule according to the invention, having a reporter molecule associated therewith may be utilised in immunoassays. Such immunoassays include, but are not limited to, radioimmunoassays (RIAs), enzyme-linked immunosorbent assays (ELISAs) and immunochromatographic techniques (ICTs), Western blotting which are well known those of skill in the art. For example, reference may be made to Coligan *et al.* (1994, *supra*) which discloses a variety of immunoassays that may be used in accordance with the present invention. Immunoassays may include competitive assays as understood in the art or as for example described *infra*. It will be understood that the present invention encompasses qualitative and quantitative immunoassays.

Suitable immunoassay techniques are described for example in US Patent Nos. 4,016,043, 4, 424,279 and 4,018,653. These include both single-site and two-site assays of the non-competitive types, as well as the traditional competitive binding assays. These assays also include direct binding of a labelled antigen-binding molecule to a target antigen.

Two site assays are particularly favoured for use in the present invention. A number of variations of these assays exist, all of which are intended to be encompassed by the present invention. Briefly, in a typical forward assay, an unlabelled antigen-binding molecule such as an unlabelled antibody is immobilised on a solid substrate and the sample to be tested brought into contact with the bound molecule. After a suitable period of incubation, for a period of time sufficient to allow formation of an antibody-antigen complex, another antigen-binding molecule, suitably a second antibody specific to the antigen, labelled with a reporter molecule capable of producing a detectable signal is then added and incubated, allowing time sufficient for the formation of another complex of antibody-antigen-labelled antibody. Any unreacted material is washed away and the presence of the antigen is determined by observation of a signal produced by the reporter

molecule. The results may be either qualitative, by simple observation of the visible signal, or may be quantitated by comparing with a control sample containing known amounts of antigen. Variations on the forward assay include a simultaneous assay, in which both sample and labelled antibody are added simultaneously to the bound antibody. These techniques are well known to those skilled in the art, including minor variations as will be readily apparent. In accordance with the present invention, the sample is one that might contain an antigen including a tissue or fluid as described above.

In the typical forward assay, a first antibody having specificity for the antigen or antigenic parts thereof is either covalently or passively bound to a solid surface. The solid surface is typically glass or a polymer, the most commonly used polymers being cellulose, polyacrylamide, nylon, polystyrene, polyvinyl chloride or polypropylene. The solid supports may be in the form of tubes, beads, discs or microplates, or any other surface suitable for conducting an immunoassay. The binding processes are well known in the art and generally consist of cross-linking, covalently binding or physically adsorbing, the polymer-antibody complex to the solid support, which is then washed in preparation for the test sample. An aliquot of the sample to be tested is then added to the solid phase complex and incubated for a period of time sufficient and under suitable conditions to allow binding of any antigen present to the antibody. Following the incubation period, the antigen-antibody complex is washed and dried and incubated with a second antibody specific for a portion of the antigen. The second antibody has generally a reporter molecule associated therewith that is used to indicate the binding of the second antibody to the antigen. The amount of labelled antibody that binds, as determined by the associated reporter molecule, is proportional to the amount of antigen bound to the immobilised first antibody.

An alternative method involves immobilising the antigen in the biological sample and then exposing the immobilised antigen to specific antibody that may or may not be labelled with a reporter molecule. Depending on the amount of target and the strength of the reporter molecule signal, a bound antigen may be detectable by direct labelling with the antibody. Alternatively, a second labelled antibody, specific to the first antibody is exposed to the target-first antibody complex to form a target-first antibody-second

antibody tertiary complex. The complex is detected by the signal emitted by the reporter molecule.

From the foregoing, it will be appreciated that the reporter molecule associated with the antigen-binding molecule may include the following:

(a) direct attachment of the reporter molecule to the antigen-binding molecule;

(b) indirect attachment of the reporter molecule to the antigen-binding molecule; *i.e.*, attachment of the reporter molecule to another assay reagent which subsequently binds to the antigen-binding molecule; and

(c) attachment to a subsequent reaction product of the antigen-binding molecule.

The reporter molecule may be selected from a group including a chromogen, a catalyst, an enzyme, a fluorochrome, a chemiluminescent molecule, a lanthanide ion such as Europium (Eu^{34}), a radioisotope and a direct visual label.

In the case of a direct visual label, use may be made of a colloidal metallic or non-metallic particle, a dye particle, an enzyme or a substrate, an organic polymer, a latex particle, a liposome, or other vesicle containing a signal producing substance and the like.

A large number of enzymes suitable for use as reporter molecules is disclosed in United States Patent Specifications U.S. 4,366,241, U.S. 4,843,000, and U.S. 4,849,338. Suitable enzymes useful in the present invention include alkaline phosphatase, horseradish peroxidase, luciferase, β-galactosidase, glucose oxidase, lysozyme, malate dehydrogenase and the like. The enzymes may be used alone or in combination with a second enzyme that is in solution.

Suitable fluorochromes include, but are not limited to, fluorescein isothiocyanate (FITC), tetramethylrhodamine isothiocyanate (TRITC), R-Phycoerythrin (RPE), and Texas Red. Other exemplary fluorochromes include those discussed by Dower *et al.* (International Publication WO 93/06121). Reference also may be made to the fluorochromes described in U.S. Patents 5,573,909 (Singer *et al*), 5,326,692 (Brinkley *et al*). Alternatively, reference may be made to the fluorochromes described in U.S. Patent Nos. 5,227,487, 5,274,113, 5,405,975, 5,433,896, 5,442,045, 5,451,663, 5,453,517, 5,459,276, 5,516,864, 5,648,270 and 5,723,218.

In the case of an enzyme immunoassay, an enzyme is conjugated to the second antibody, generally by means of glutaraldehyde or periodates. As will be readily recognised, however, a wide variety of different conjugation techniques exist which are readily available to the skilled artisan. The substrates to be used with the specific enzymes are generally chosen for the production of, upon hydrolysis by the corresponding enzyme, a detectable colour change. Examples of suitable enzymes include those described *supra*. It is also possible to employ fluorogenic substrates, which yield a fluorescent product rather than the chromogenic substrates noted above. In all cases, the enzyme-labelled antibody is added to the first antibody-antigen complex. It is then allowed to bind, and excess reagent is washed away. A solution containing the appropriate substrate is then added to the complex of antibody-antigen-antibody. The substrate will react with the enzyme linked to the second antibody, giving a qualitative visual signal, which may be further quantitated, usually spectrophotometrically, to give an indication of the amount of antigen which was present in the sample.

Alternately, fluorescent compounds, such as fluorescein, rhodamine and the lanthanide, europium (EU), may be chemically coupled to antibodies without altering their binding capacity. When activated by illumination with light of a particular wavelength, the fluorochrome-labelled antibody adsorbs the light energy, inducing a state to excitability in the molecule, followed by emission of the light at a characteristic colour visually detectable with a light microscope. The fluorescent-labelled antibody is allowed to bind to the first antibody-antigen complex. After washing off the unbound reagent, the remaining tertiary complex is then exposed to light of an appropriate wavelength. The fluorescence observed indicates the presence of the antigen of interest. Immunofluorometric assays (IFMA) are well established in the art. However, other reporter molecules, such as radioisotope, chemiluminescent or bioluminescent molecules may also be employed.

It will be well understood that other means of testing target polypeptide (*e.g.*, Pyk, NlpD, CPn0585) levels are available, including, for instance, those involving testing for an altered level of the target polypeptide binding activity to the target polypeptide binding partner, or Western blot analysis of target protein levels in tissues, cells or fluids using anti-target protein antigen-binding molecules, or assaying the amount of antigen-binding

molecule or other target polypeptide binding partner which is not bound to a sample, and subtracting from the total amount of antigen-binding molecule or binding partner added.

Alternatively, the presence of a chlamydial infection may be detected by assaying a patient's immune response to chlamydial antigens, particularly those antigens that are expressed at higher levels in, or whose presence is associated with, the persistent phase of the chlamydial developmental cycle. Components of the patient's immune system whose activity may be assayed include, but are not limited to, antibodies, B cells, T cells, dendritic cells and macrophages. For example, an immune response can be measured by standard tests including: direct measurement of peripheral blood lymphocytes by means known to the art; natural killer cell cytotoxicity assays (see, *e.g.*, Provinciali M. *et al* (1992, *J. Immunol. Meth.* **155**: 19-24), cell proliferation assays (see, *e.g.*, Vollenweider, I. And Groseurth, P. J. (1992, *J. Immunol. Meth.* **149**: 133-135), immunoassays of immune cells and subsets (see, *e.g.*, Loeffler, D. A., *et al.* (1992, *Cytom.* **13**: 169-174); Rivoltini, L., *et al.* (1992, *Can. Immunol. Immunother.* **34**: 241-251); or skin tests for cell-mediated immunity (see, *e.g.*, Chang, A. E. et al (1993, *Cancer Res.* **53**: 1043-1050). CTL lysis assays may also be employed using stimulated splenocytes or peripheral blood mononuclear cells (PBMC) on peptide coated or recombinant virus infected cells using ^{51}Cr or Alamar Blue™ labeled target cells. Such assays can be performed using for example primate, mouse or human cells (Allen *et al.*, 2000, *J. Immunol.* **164**(9): 4968-4978 also Woodberry *et al.*, *infra*). In a preferred embodiment, the presence of a persistent chlamydial organism is detected by detecting antibodies to persistent phase antigens (*i.e.*, whose presence or overexpression is associated with the persistent phase of the chlamydial developmental cycle). Suitably, such detection is facilitated by screening sera of a patient with a recombinant persistent phase antigen or portion thereof (*e.g.*, by ELISA assay or by Western blot) for the presence of specific antibodies (IgG, IgM, IgA or IgE) that are immuno-interactive with that antigen or portion.

9. Therapeutic and prophylactic uses

The modulating agents of the invention prepared, for example, according to methods described in Section 3 *supra* have utility in compositions for treating and or preventing chlamydial infections, particularly chronic or persistent chlamydial infections.

Accordingly, the present invention encompasses a method for treatment and/or prophylaxis of a chronic chlamydial infection by administering to a patient in need thereof an effective amount of agent, which specifically targets the persistent phase of the chlamydial developmental cycle, for a time and under conditions sufficient to treat and/or prevent the infection. In accordance with the present invention, the agent will modulate the expression of a gene or the level and/or functional activity of an expression product of said gene, wherein the gene is selected from *pyk*, *nlpD*, *Cpn0585*, or a gene belonging to the same regulatory or biosynthetic pathway as *pyk*, *nlpD*, *Cpn0585*, *ompA*, *ompB*, *hsp60* or as a gene involved in the biosynthesis of LPS, or a variant of said gene. In one embodiment, the agent is effective in killing or otherwise impairing or attenuating a chlamydial organism in the persistent phase of its developmental cycle.

In another embodiment, the agent is effective in causing said organism to revert or otherwise enter the lytic phase of its developmental cycle. In this embodiment, the invention contemplates the use of a second agent which modulates the expression of a gene associated with the lytic phase of said developmental cycle or the level and/or functional activity of an expression product of that gene. Indeed, a combination treatment which targets both the persistent state and also the lytic state is likely to be the most effective in eliminating chlamydial infection (particularly the chronic / persistent state) and hence substantially preventing chlamydial disease outcomes. Accordingly, the invention is also directed to a method for treating and/or preventing a chronic or lytic infection caused by chlamydial organism, comprising sequentially or simultaneously administering to a patient of a first agent and a second agent, wherein the first agent, which modulates the expression of a first gene expressed in the persistent phase of the developmental cycle of organism, or the level and/or functional activity of an expression product of said first gene, is administered to the patient for a time and under conditions sufficient to cause said organism to enter the lytic phase of said developmental cycle and wherein the second agent, which modulates the expression of a second gene associated with the lytic phase of said developmental cycle or the level and/or functional activity of an expression product of said second gene, is also administered to the patient for a time and under conditions sufficient to kill or otherwise inactivate or attenuate said organism.

The second agent is preferably an antibiotic that acts on actively replicating chlamydial organisms and that is, therefore, effective in killing or otherwise impairing or attenuating said chlamydial organism in the lytic phase of its developmental cycle. Any suitable antibiotics are contemplated by the present invention and include, but are not limited to, tetracycline, erythromycin, azithromycin, ofloxacin, ciprofloxin or prodrugs or analogues thereof.

The invention also envisions a composition for treatment and/or prophylaxis of chronic chlamydial infection, comprising a modulatory agent as broadly described above, together with a pharmaceutically acceptable carrier.

The modulatory agent(s) can be administered to a patient either by themselves, or in pharmaceutical compositions where they are mixed with suitable pharmaceutically acceptable carrier. Depending on the specific conditions being treated, modulatory agents may be formulated and administered systemically or locally. Techniques for formulation and administration may be found in "Remington's Pharmaceutical Sciences," Mack Publishing Co., Easton, Pa., latest edition. Suitable routes may, for example, include oral, rectal, transmucosal, or intestinal administration; parenteral delivery, including intramuscular, subcutaneous, intramedullary injections, as well as intrathecal, direct intraventricular, intravenous, intraperitoneal, intranasal, or intraocular injections. For injection, the agents of the invention may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks' solution, Ringer's solution, or physiological saline buffer. For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art. Intra-muscular and subcutaneous injection is appropriate, for example, for administration of immunogenic compositions, vaccines and DNA vaccines. Preferably, but not essentially, the composition is administered intranasally, orally and/or intragastrically and preferably in association with a mucosal adjuvant as for example described herein.

The agents can be formulated readily using pharmaceutically acceptable carriers well known in the art into dosages suitable for oral administration. Such carriers enable the compounds of the invention to be formulated in dosage forms such as tablets, pills, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated. These carriers may be selected from sugars, starches, cellulose and its

derivatives, malt, gelatine, talc, calcium sulphate, vegetable oils, synthetic oils, polyols, alginic acid, phosphate buffered solutions, emulsifiers, isotonic saline, and pyrogen-free water.

Pharmaceutical compositions suitable for use in the present invention include compositions wherein the active ingredients are contained in an effective amount to achieve its intended purpose. The dose of agent administered to a patient should be sufficient to effect a beneficial response in the patient over time such as a reduction or attenuation of a chlamydial infection. The quantity of the agent(s) to be administered may depend on the subject to be treated inclusive of the age, sex, weight and general health condition thereof. In this regard, precise amounts of the agent(s) for administration will depend on the judgement of the practitioner. In determining the effective amount of the agent to be administered in the treatment or prophylaxis of the chronic chlamydial infection, the physician may evaluate fluid or tissue levels of a target molecule of the invention, and progression of the disorder. In any event, those of skill in the art may readily determine suitable dosages of the agents of the invention.

Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances that increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilisers or agents that increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

Pharmaceutical preparations for oral use can be obtained by combining the active compounds with solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as., for example, maize starch, wheat starch, rice starch, potato starch, gelatine, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or

polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate. Such compositions may be prepared by any of the methods of pharmacy but all methods include the step of bringing into association one or more agents as described above with the carrier which constitutes one or more necessary ingredients. In general, the pharmaceutical compositions of the present invention may be manufactured in a manner that is itself known, *e.g.*, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilising processes.

Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterise different combinations of active compound doses.

Pharmaceutical preparations that can be used orally include push-fit capsules made of gelatine, as well as soft, sealed capsules made of gelatine and a plasticiser, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilisers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilisers may be added.

Dosage forms of the modulatory agents of the invention may also include injecting or implanting controlled releasing devices designed specifically for this purpose or other forms of implants modified to act additionally in this fashion. Controlled release of an agent of the invention may be effected by coating the same, for example, with hydrophobic polymers including acrylic resins, waxes, higher aliphatic alcohols, polylactic and polyglycolic acids and certain cellulose derivatives such as hydroxypropylmethyl cellulose. In addition, controlled release may be effected by using other polymer matrices, liposomes and/or microspheres.

Modulating agents of the invention may be provided as salts with pharmaceutically compatible counterions. Pharmaceutically compatible salts may be formed with many acids, including but not limited to hydrochloric, sulfuric, acetic, lactic, tartaric, malic, succinic, *etc.* Salts tend to be more soluble in aqueous or other protonic solvents that are the corresponding free base forms.

For any compound used in the method of the invention, the therapeutically effective dose can be estimated initially from cell culture assays. For example, a dose can be formulated in animal models to achieve a circulating concentration range that includes the IC50 as determined in cell culture (*e.g.*, the concentration of a test agent, which achieves a half-maximal inhibition of the activity or level of a target molecule of the invention). Such information can be used to more accurately determine useful doses in humans.

Toxicity and therapeutic efficacy of such agents can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, for determining the LD50 (the dose lethal to 50% of the population) and the ED50 (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD50/ED50. Compounds which exhibit large therapeutic indices are preferred. The data obtained from these cell culture assays and animal studies can be used in formulating a range of dosage for use in human. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED50 with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilised. The exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's condition. (See for example Fingl *et al.*, 1975, in "The Pharmacological Basis of Therapeutics", Ch. 1 p1).

Dosage amount and interval may be adjusted individually to provide plasma levels of the active agent which are sufficient to maintain target molecule-inhibitory effects or target molecule activating or stabilising effects. Usual patient dosages for systemic administration range from 1-2000 mg/day, commonly from 1-250 mg/day, and typically from 10-150 mg/day. Stated in terms of patient body weight, usual dosages range from 0.02-25 mg/kg/day, commonly from 0.02-3 mg/kg/day, typically from 0.2-1.5 mg/kg/day.

Stated in terms of patient body surface areas, usual dosages range from 0.5-1200 mg/m^2/day, commonly from 0.5-150 mg/m^2/day, typically from 5-100 mg/m^2/day.

Alternately, one may administer the compound in a local rather than systemic manner, for example, *via* injection of the compound directly into a tissue, often in a depot or sustained release formulation.

Furthermore, one may administer the drug in a targeted drug delivery system, for example, in a liposome coated with an epithelium-specific antibody. The liposomes will be targeted to and taken up selectively by a particular epithelium such as mucosal epithelium.

In cases of local administration or selective uptake, the effective local concentration of the agent may not be related to plasma concentration.

In an alternate embodiment, a polynucleotide encoding a modulatory agent of the invention may be used as a therapeutic or prophylactic composition in the form of a "naked DNA" composition as is known in the art. For example, an expression vector comprising said polynucleotide operably linked to a regulatory polynucleotide (*e.g.* a promoter, transcriptional terminator, enhancer *etc*) may be introduced into an animal where it causes production of a modulatory agent *in vivo*, particular in epithelial tissue. The modulatory agent in this instance may be an antisense molecule or ribozyme.

The step of introducing the expression vector into a target cell will differ depending on the intended use and species, and can involve one or more of non-viral and viral vectors, cationic liposomes, retroviruses, and adenoviruses such as, for example, described in Mulligan, R.C., (1993 *Science* **260**: 926-932. Such methods can include, for example:

Local application of the expression vector by injection (Wolff *et al.*, 1990, *Science* **247**: 1465-1468), surgical implantation, instillation or any other means. This method can also be used in combination with local application by injection, surgical implantation, instillation or any other means, of cells responsive to the protein encoded by the expression vector so as to increase the effectiveness of that treatment. This method can also be used in combination with local application by injection, surgical implantation,

instillation or any other means, of another factor or factors required for the activity of said protein.

General systemic delivery by injection of DNA, (Calabretta *et al.*, 1993, *Cancer Treat. Rev.* **19**: 169-179), or RNA, alone or in combination with liposomes (Zhu *et al.*, 1993, *Science* **261**: 209-212), viral capsids or nanoparticles (Bertling *et al.*, 1991, *Biotech. Appl. Biochem.* **13**: 390-405) or any other mediator of delivery. Improved targeting might be achieved by linking the polynucleotide/expression vector to a targeting molecule (the so-called "magic bullet" approach employing, for example, an antigen-binding molecule), or by local application by injection, surgical implantation or any other means, of another factor or factors required for the activity of the protein encoded by said expression vector, or of cells responsive to said protein.

Injection or implantation or delivery by any means, of cells that have been modified *ex vivo* by transfection (for example, in the presence of calcium phosphate: Chen *et al.*, 1987, *Mole. Cell Biochem.* **7**: 2745-2752, or of cationic lipids and polyamines: Rose *et al.*, 1991, *BioTech.* **10**: 520-525), infection, injection, electroporation (Shigekawa *et al.*, 1988, *BioTech.* **6**: 742-751) or any other way so as to increase the expression of said polynucleotide in those cells. The modification can be mediated by plasmid, bacteriophage, cosmid, viral (such as adenoviral or retroviral; Mulligan, 1993, *Science* **260**: 926-932; Miller, 1992, *Nature* **357**: 455-460; Salmons *et al.*, 1993, *Hum. Gen. Ther.* **4**: 129-141) or other vectors, or other agents of modification such as liposomes (Zhu *et al.*, 1993, *Science* **261**: 209-212), viral capsids or nanoparticles (Bertling *et al.*, 1991, *Biotech. Appl. Biochem.* **13** 390-405), or any other mediator of modification. The use of cells as a delivery vehicle for genes or gene products has been described by Barr *et al.*, 1991, *Science* **254**: 1507-1512 and by Dhawan *et al.*, 1991, *Science* **254** 1509-1512. Treated cells can be delivered in combination with any nutrient, growth factor, matrix or other agent that will promote their survival in the treated subject.

The present invention also encompasses a method for treatment and/or prophylaxis of a chronic infection caused by an organism of the Chlamydiaceae family in a patient by administering to said patient an immunopotentiating agent selected from a proteinaceous molecule comprising at least a portion of a polypeptide, or variant or derivative thereof, associated with the persistent phase of the developmental cycle of said

organism, or a polynucleotide from which said proteinaceous molecule is expressed. Examples of such persistent phase-associated antigens include, but are not restricted to, a polypeptide encoded by *pyk*, *nlpD*, *Cpn0585*, or a gene that is upregulated and belonging to the same regulatory or biosynthetic pathway as *pyk*, *nlpD*, *Cpn0585*, *ompA*, *ompB*, *hsp60* or as a gene involved in the biosynthesis of LPS, or a variant of said gene, or a biologically portion of said polypeptide, or an expression vector comprising a polynucleotide encoding a said polypeptide or fragment, operably linked to a transcriptional regulatory element.

The invention further contemplates a method for treatment and/or prophylaxis of a lytic or chronic infection caused by an organism of the Chlamydiaceae family in a patient by sequentially or simultaneously administering to said patient effective amounts of a first immunopotentiating agent and a second immunopotentiating agent. The first immunopotentiating agent is suitably selected from a first proteinaceous molecule comprising at least a portion of a polypeptide, or variant or derivative thereof, associated with the persistent phase of the developmental cycle of said organism, or a polynucleotide from which said first proteinaceous molecule is expressed. The second immunopotentiating agent is suitably selected from a second proteinaceous molecule comprising at least a portion of a polypeptide, or a variant or derivative thereof, associated with the lytic phase of said developmental cycle, or a polynucleotide from which said second proteinaceous molecule is expressed. Any suitable lytic phase antigens may be used in this regard. In a preferred embodiment, the lytic phase antigen is MOMP or a biologically active fragment thereof, or an expression vector comprising a polynucleotide encoding said MOMP or said fragment, operably linked to a transcriptional regulatory element.

Thus, the combination of a persistent phase antigen and a lytic phase antigen may be used as actives in the preparation of immunopotentiating compositions or vaccines. Such preparation uses routine methods known to persons skilled in the art. Exemplary procedures include, for example, those described in NEW GENERATION VACCINES (1997, Levine *et al.*, Marcel Dekker, Inc. New York, Basel Hong Kong). Typically, immunopotentiating compositions are prepared as injectables, either as liquid solutions or suspensions; solid forms suitable for solution in, or suspension in, liquid prior to injection

may also be prepared. The preparation may also be emulsified. The active immunogenic ingredients are often mixed with excipients that are pharmaceutically acceptable and compatible with the active ingredient. Suitable excipients are, for example, water, saline, dextrose, glycerol, ethanol, or the like and combinations thereof. In addition, if desired, the immunopotentiating composition or vaccine may contain minor amounts of auxiliary substances such as wetting or emulsifying agents, pH buffering agents, and/or adjuvants that enhance the effectiveness of the composition.

A polypeptide, fragment, variant or derivative of the invention according to the invention can be mixed, conjugated or fused with other antigens, including B or T cell epitopes of other antigens. In addition, it can be conjugated to a carrier as described below.

When an haptenic peptide is used (*i.e.*, a peptide which reacts with cognate antibodies, but cannot itself elicit an immune response), it can be conjugated with an immunogenic carrier. Useful carriers are well known in the art and include for example: thyroglobulin; albumins such as human serum albumin; toxins, toxoids or any mutant crossreactive material (CRM) of the toxin from tetanus, diphtheria, pertussis, *Pseudomonas*, *E. coli*, *Staphylococcus*, and *Streptococcus*; polyamino acids such as poly(lysine:glutamic acid); influenza; Rotavirus VP6, Parvovirus VP1 and VP2; hepatitis B virus core protein; hepatitis B virus recombinant vaccine and the like. Alternatively, a fragment or epitope of a carrier protein or other immunogenic protein may be used. For example, a haptenic peptide can be coupled to a T cell epitope of a bacterial toxin, toxoid or CRM. In this regard, reference may be made to U.S. Patent No 5,785,973.

In addition, a polypeptide, fragment, variant or derivative of the invention may act as a carrier protein in vaccine compositions directed against an organism of the Chlamydiaceae family.

The immunopotentiating compositions of the invention may be administered as multivalent subunit compositions or vaccines in combination with other chlamydial immunogens such as MOMP. Alternatively, or additionally, they may be administered in concert with immunologically active antigens against other pathogenic species such as, for

example, the pathogenic bacteria *H. influenzae*, *M. catarrhalis*, *N. gonorrhoeae*, *E. coli*, *S. pneumoniae* etc.

The immunopotentiating compositions may include an adjuvant as is well known in the art. Suitable adjuvants include, but are not limited to: surface active substances such as hexadecylamine, octadecylamine, octadecyl amino acid esters, lysolecithin, dimethyldioctadecylammonium bromide, N, N-dicoctadecyl-N', N'bis(2-hydroxyethyl-propanediamine), methoxyhexadecylglycerol, and pluronic polyols; polyamines such as pyran, dextransulfate, poly IC carbopol; peptides such as muramyl dipeptide and derivatives such as N-acetyl-muramyl-L-threonyl-D-isoglutamine (thur-MDP), N-acetyl-nor-muramyl-L-alanyl-D-isoglutamine (CGP 11637, referred to as nor-MDP), N-acetylmuramyl-L-alanyl-D-isoglutaminyl-L-alanine-2-(1'-2'-dipalmitoyl-sn-glycero-3-hydroxyphosphoryloxy)-ethylamine (CGP 1983A, referred to as MTP-PE); dimethylglycine, tuftsin; oil emulsions; and mineral gels such as aluminum phosphate, aluminum hydroxide or alum; Freunds incomplete adjuvant, Freunds complete adjuvant, tetanus toxoid, diphtheria toxoid, ISCOMS, QuilA, and RIBI, which contains three components extracted from bacteria, monophosphoryl lipid A, trehalose dimycolate and cell wall skeleton (MPL+TDM+CWS) in a 2% squalene/Tween 80 emulsion. lymphokines, and QuilA. The effectiveness of an adjuvant may be determined for example by measuring the amount of antibodies resulting from the administration of the composition, wherein those antibodies are directed against one or more said chlamydial antigens or by measuring antigen specific T cell proliferation or cytolytic activity.

In a preferred embodiment, the immunopotentiating composition is administered *via* a mucosal route such as, but not limited to, orally, urogenitally or transdermally or combination of these. Accordingly, the adjuvant is preferably a mucosal adjuvant. Preferably, the mucosal adjuvant is cholera toxin or diphtheria toxin. Mucosal adjuvants other than cholera toxin or diphtheria toxin which may be used in accordance with the present invention include non-toxic derivatives of said toxins, such as the B sub-unit (CTB), chemically modified cholera or diphtheria toxin, or related proteins produced by modification of the cholera toxin or diphtheria toxin amino acid sequence. These may be added to, or conjugated with, the polypeptides, fragments, variants or derivatives of the invention. The same techniques can be applied to other molecules with mucosal adjuvant

or delivery properties such as *Escherichia coli* heat labile toxin. Other compounds with mucosal adjuvant or delivery activity may be used such as bile; polycations such as DEAE-dextran and polyornithine; detergents such as sodium dodecyl benzene sulphate; lipid-conjugated materials; antibiotics such as streptomycin; vitamin A; and other compounds that alter the structural or functional integrity of mucosal surfaces. Other mucosally active compounds include derivatives of microbial structures such as MDP; acridine and cimetidine.

The immunogenic agents of the invention may be delivered in ISCOMS (immune stimulating complexes), ISCOMS containing CTB, liposomes or encapsulated in compounds such as acrylates or poly(DL-lactide-co-glycoside) to form microspheres of a size suited to adsorption by M cells. Alternatively, micro or nanoparticles may be covalently attached to molecules, which have specific epithelial receptors. The polypeptide, fragments, variant or derivative of the invention may also be incorporated into oily emulsions and delivered orally. An extensive though not exhaustive list of adjuvants can be found in Cox and Coulter (Cox and Coulter, 1992, Advances in adjuvant technology and application. In *Animal Parasite Control Using Biotechnology*. Edited by W.K.Yong. Published by CRC Press).

In another embodiment, the adjuvant is an antigen-presenting cell, preferably a dendritic cell, which presents a processed persistent phase or lytic phase antigen on its surface. Such adjuvants may be prepared by contacting an antigen-presenting cell with a persistent phase or lytic phase antigen for a time and under conditions sufficient to allow said antigen to be internalised and processed by said antigen-presenting cell for presentation to said B lymphocytes and said T lymphocytes. A variety of different strategies can be used for improving delivery of exogenous antigen to the endogenous processing pathway of antigen-presenting cells, particularly of dendritic cells. These methods include insertion of antigen in pH-sensitive liposomes (Zhou and Huang, 1994, *Immunomethods*, **4**: 229-235), osmotic lysis of pinosomes after pinocytic uptake of soluble antigen (Moore *et al.*, 1988, *Cell*, **54**; 777-785), and coupling of antigens to potent adjuvants (Aichele *et al.*, 1990, *J. Exp. Med.*, **171**: 1815-1820; Gao *et al.*, 1991, *J. Immunol.*, **147**: 3268-3273; Schulz *et al.*, 1991, *Proc. Natl. Acad. Sci. USA*, **88**: 991-993; Kuzu *et al.*, 1993, *Euro. J. Immunol.*, **23**: 1397-1400; and Jondal *et al.*, 1996, *Immunity* **5**:

295-302). Adjuvants (*e.g.*, Freund's adjuvant) can also be used to assist in the internalisation and presentation of processed antigen onto the surface of the antigen-presenting cells.

The polypeptides, fragments, variants or derivatives of the invention may be expressed by attenuated viral hosts. A virus may be rendered substantially avirulent by any suitable physical (*e.g.*, heat treatment) or chemical means (*e.g.*, formaldehyde treatment). Ideally, the infectivity of the virus is destroyed without affecting the proteins that carry the immunogenicity of the virus. From the foregoing, it will be appreciated that attenuated viral hosts may comprise live viruses or inactivated viruses.

Attenuated viral or bacterial hosts which may be useful in a vaccine according to the invention may comprise viral vectors inclusive of adenovirus, cytomegalovirus and preferably pox viruses such as vaccinia (see for example Paoletti and Panicali, U.S. Patent No. 4,603,112) and attenuated *Salmonella* strains (see for example Stocker, U.S. Patent No. 4,550,081).

Live vaccines are particularly advantageous because they lead to a prolonged stimulus that can confer substantially long-lasting immunity. Thus, as an alternative to the delivery of immunogenic agents in the form of a therapeutic or prophylactic immunopotentiating composition, these agents may be delivered to the host using a live vaccine vector, in particular using live recombinant bacteria, viruses or other live agents, containing the genetic material necessary for the expression of the polypeptide, fragment, variant or derivative of the invention as a foreign antigen.

Multivalent immunopotentiating compositions or vaccines can be prepared from one or more organisms of the Chlamydiaceae family that express different persistent phase antigens or epitopes. In addition, epitopes of other pathogenic microorganisms can be incorporated into the compositions.

In a preferred embodiment, this will involve the construction of a recombinant vaccinia virus to express a nucleic acid sequence according to the invention. Upon introduction into a host, the recombinant vaccinia virus expresses the immunogenic agent, and thereby elicits a host CTL response. For example, reference may be made to U.S.

Patent No 4,722,848, which describes vaccinia vectors and methods useful in immunisation protocols. A variety of other vectors useful for therapeutic administration or immunisation with the immunogenic agents of the invention will be apparent to those skilled in the art from the present disclosure.

In a further embodiment, a polynucleotide of the invention may be used as a vaccine in the form of a "naked DNA" vaccine as is known in the art. For example, an expression vector of the invention may be introduced into a mammal, where it causes production of a polypeptide *in vivo*, against which the host mounts an immune response as for example described in Barry, M. *et al.*, (1995, *Nature*, **377**:632-635). Thus, the invention also contemplates nucleic acid-based immunopotentiating compositions comprising an expression vector including a polynucleotide encoding an at least one antigen selected from persistent phase chlamydial antigens or lytic phase chlamydial antigens, wherein said polynucleotide is operably linked to a regulatory polynucleotide, together with a pharmaceutically acceptable carrier.

With regard to nucleic acid based compositions, all modes of delivery of such compositions are contemplated by the present invention. Delivery of these compositions to cells or tissues of an animal may be facilitated by microprojectile bombardment, liposome mediated transfection (*e.g.*, lipofectin or lipofectamine), electroporation, calcium phosphate or DEAE-dextran-mediated transfection, for example. In an alternate embodiment, a synthetic construct may be used as a therapeutic or prophylactic composition in the form of a "naked DNA" composition as is known in the art. A discussion of suitable delivery methods may be found in Chapter 9 of CURRENT PROTOCOLS IN MOLECULAR BIOLOGY (Eds. Ausubel *et al.*; John Wiley & Sons Inc., 1997 Edition) or on the Internet site DNAvaccine.com. The compositions may be administered by intradermal (*e.g.*, using panjet™ delivery) or intramuscular routes.

The immunopotentiating compositions will suitably elicit a B cell response and preferably a T cell response. Immunopotentiating compositions which produce a desired immune response can be evaluated using animal models of chlamydial infection (*e.g.*, mouse for both urogenital and respiratory and cardiovascular infections; guinea pig for predominantly urogenital infections). The selected animal model is suitably be vaccinated (*e.g.*, *via* several mucosal routes) using either full length recombinant proteins or portions

thereof and boosted after 4-6 weeks. The immune response (preferably both antibody and cell mediated) is typically measured at weekly intervals. Generally, after periods of 8 weeks and 6 months, the vaccinated as well as unvaccinated control animals, are challenged with live Chlamydia. The immune responses (preferably both antibody and cell mediated) are continued to be measured at weekly intervals. Typically, several animals from each group are sacrificed and the status of disease evaluated, after 3 and 6 months and compared with unvaccinated controls.

In order that the invention may be readily understood and put into practical effect, particular preferred embodiments will now be described by way of the following non-limiting examples.

EXAMPLES

EXAMPLE 1

Altered morphological forms observed in IFN-δ-treated C. pneumoniae *cultures*

Normal (ie not treated with IFN-δ) cultures of *C. pneumoniae* IOL-207 contained characteristic membrane-bound inclusions approximately 5-8 μm in diameter, tightly packed with chlamydial particles. EBs were electron opaque, 200-400 nm, spherical-oval shaped particles with little periplasmic space and surrounded by an undulating cell membrane (Figure 1a). RBs were round to oval in shape, 600-900 nm in diameter, with a typical electron translucent centre and condensed cytoplasm towards the periphery (Figure 1a). By comparison, the IFN-δ-treated cultures, in addition to containing large numbers of morphologically normal inclusions with normal EBs and RBs, also contained 10-20% of forms exhibiting abnormal morphology (Figure 1b). These abnormal inclusions were smaller (3.5 μm in diameter) than normal inclusions and contained considerably lower numbers of chlamydial particles. There were often pronounced extra-cellular spaces evident in these persistent inclusions. While the EBs in these inclusions appeared morphologically normal, the RBs were enlarged (400 x 900 nm) compared to those in normal inclusions (300 x 600 nm) and were pleomorphic, being either elongated with evidence of abnormal budding or branching occurring, or showing multi-layered membranes.

Methods

C. pneumoniae cell culture conditions

HEp2 cells were grown in 75cm^2 flasks at 37° C in 5% CO_2 and maintained in complete DMEM consisting of Dulbecco's Minimum Essential Medium (Life Technologies) supplemented with 10% foetal bovine serum (CSL), 2mM L-glutamine (Life Technologies), 100(g/mL streptomycin sulphate (Life Technologies) and 2 U/mL gentamycin (Life Technologies). *C. pneumoniae* IOL207 inoculum was generated by lysing 2x10^7 infected cells (20-30% infected cell monolayer, 96 hours post-infection) in 20ml SPG (0.22 M sucrose, 0.01 M phosphate, 0.0005 M L-glutamic acid) by the addition

of $1 cm^3$ sterile glass beads followed by mechanical shaking plus bath sonication. The lysate was centrifuged at 1000g for 5 minutes and the supernatant aliquoted and stored at – 80° C.

C. pneumoniae infections for both RNA extraction and transmission electron microscopy (TEM) were established by replacing the growth medium of confluent Hep2 monolayers with 1 mL of chlamydial inoculum and 4ml of complete DMEM followed by centrifugation at 1700g for 30 minutes. The cells were subsequently incubated at 37° C in 5% CO_2 for 6 hours, after which the inoculum was replaced with 10 mL complete DMEM containing 1 μg/mL cycloheximide in the presence (IFN-treated, I) or absence (untreated, N) of either 100 U/mL (for RNA extraction) or 10 U/mL (for TEM) of human interferon-gamma (Life Technologies). Cultures were grown for a further 18 hours (total of 24 hours post-infection) after which time half the samples were removed for analysis and half the samples had the media replaced (as above) and incubation continued until 48 hours post-infection. Samples for RNA extraction were washed twice with 5ml Hanks buffered saline solution (Life Technologies) before the addition of 6 mL Tri-reagent (Sigma) and storage at -80°C until RNA isolation. Samples for TEM were fixed in 3% glutaraldehyde in 0.1 M cacodylate buffer, osmotically adjusted to approximately 320 milliosmoles with sucrose and $CaCl_2$.

Transmission Electron Microscopy

Fixed samples for TEM were scraped from culture flasks and transferred to 1.5 ml micro-centrifuge tubes for further processing. After post-fixation in osmium tetroxide, followed by uranyl acetate, samples were dehydrated in increasing grades of ethanol (50, 70, 90%) and acetone (90, 100%) prior to infiltration and embedding in Spurr epoxy resin. Ultra-thin sections (approx. 90 nm) were collected onto 200 mesh copper grids and contrasted with 1% uranyl acetate and Reynold's lead citrate. Sections were examined and photographed using a JEOL 1200EX TEM operating at 80kV.

EXAMPLE 2

Differential gene transcription in IFN-δ-treated versus normal C. pneumoniae *cultures*

A total of 14 chlamydial genes (*16SrRNA*, *ompA*, *ompB*, *omcB*, *76kDa*, *gseA*, *pmp1*, *gltX*, *hsp60*, *yaeT*, *pyk*, *nlpD*, *Cpn0585*, *Cpn1046*) were analysed by RT-PCR (and Southern blotting for the low transcript level genes) at 24 hour and 48 hours post-infection. Two genes (*16SrRNA* and *gltX*) were used as internal standards for relative comparison of gene expression between treated and non-treated cultures, at each time point. *16SrRNA* was chosen for the highly transcribed genes and *gltX* for those genes with lower levels of transcription because *16SrRNA* was thought to dominate the consumption of dNTPs from any low level transcribed gene in the same PCR reaction. In most cases, the levels of control transcript (either *16SrRNA* or *gltX*) were equal (within 10%) between the same batches of normal and IFN-δ-treated cultures, enabling direct comparison of the test genes between normal and IFN-δ-treated cultures (Figure 2). In the few instances where the levels of control transcript varied between normal and IFN-δ-treated cultures, the control levels were used to normalise the test gene results. The results for each gene were repeated in at least duplicate.

Nine genes (*16SrRNA*, *omcB*, *76kDa*, *gseA*, *pmp1*, *gltX*, *hsp60*, *yaeT*, *Cpn1046*) showed approximately equal levels of transcription in normal and IFN-δ-treated cultures (Figure 3; indicated with *). In comparison to these equally transcribed genes, five genes (*ompA*, *ompB*, *pyk*, *nlpD*, *Cpn0585*) clearly were transcribed at higher levels in the IFN-δ-treated cultures (Figure 3). While *pyk* and *nlpD* genes showed repeatable upregulation, the differences between normal and IFN-δ-treated cultures was modest. In comparison, upregulation was more evident with *ompA*, *ompB* and particularly *Cpn0585*. At the 24 hour time point, there was no evidence of any *Cpn0585* gene transcript in the normal culture whereas there was significant gene transcription evident in the IFN-δ-treated cultures. By 48 hours post-infection, some transcript was evident in the normal cultures, however the level in the IFN-δ-treated cultures was estimated to be at least 3-4 times greater.

While the intensity of the RT-PCR product may not directly reflect the actual level of gene expression, due to primer and PCR efficiency in addition to the relative

starting copy number of the transcript being amplified, we were able to estimate the temporal expression of most genes, at least in relation to the 24 hour post-infection time point. Of the genes analysed, six (*16SrRNA*, *76kDa*, *yaeT*, *ompB*, *gseA* and *Cpn1046*) were strongly transcribed at the 24 hour time point, suggestive of early-transcribed genes, three (*ompA*, *pyk* and *nlpD*) were weakly transcribed at the 24 hour time point, and the remaining three (*omcB*, *pmp1* and *Cpn0585*) were primarily transcribed late in the development cycle (ie. mainly at the 48 hour time point).

Methods

<u>Nucleic acids</u>

RNA was extracted from the samples stored in Tri-reagent (above) and contaminating DNA removed by resuspending the RNA in 130 µL 10 mM Tris-Cl (pH 7.5), 10 mM $MgCl_2$, 1mM dithioerythritol (DTE), 40 U RNase inhibitor treatment with 20 U RNase-free DNase 1 (Roche) for 30 minutes at 37° C. The RNA was further purified by processing through RNeasy mini columns (Qiagen) where 25-75 µg RNA was eluted in 50 µL of ddH_2O. Genomic DNA was extracted from *C. pneumoniae* IOL207 infected HEp2 cells (10^7) following the TRI-reagent procedure for DNA extraction (Life Technologies) yielding 100 µg total DNA. The sequences of the primers used for PCR and RT-PCR analysis were synthesised by either Life Technologies (*16SrRNA*, *ompA*, *omcB*, *ompB*, *pmp1*, *gltX*, *pyk*) or Pacific Oligos (*76kDa*, *yaeT*, *nlpD*, *groESL*, *Cpn0585*, *Cpn1046*).

<u>Analysis of gene expression</u>

10 µg of total RNA was primed with 1.0 µg of random hexamers (Roche) to generate cDNA following the method previously described (Mathews *et al.*, 1999). cDNA samples were stored at approximately 50ng/µL in 10 µL aliquots at –20° C to limit freeze/thawing. Aliquots in use were stored at 4° C between PCR assays. The presence of contaminating genomic DNA was excluded by performing PCR on RNA samples using the 16S rRNA primers.

A duplex PCR consisting of the gene of interest (Table 1) with an internal reference gene (either *16SrRNA* or *gltX*) was performed. 25 µL PCR reactions contained 1

x PCR buffer containing 1.5mM $MgCl_2$ (Roche), 1 μM of each primer, 2 mM of each dNTP (Roche), 2U Taq polymerase (Roche) and 1 μL template (either cDNA, genomic DNA or TE). PCR conditions were 94° C for 3 minutes followed by either 35 cycles (*16SrRNA* reference gene) or 40 cycles (*gltX* reference gene) of 94° C 30 seconds, 53° C 30 seconds and 72° C 45 seconds with a final extension at 72° C for 7 minutes in a Peltier PTC-200 thermal cycler (MJ Research, Watertown, Massachusetts, USA). PCR products were electrophoresed through a 2% TBE (45 mM Tris-borate, 1 mM EDTA) agarose gel containing 1 μg/mL ethidium bromide.

Southern blot analysis

Probes were generated in 50 μL reactions by incorporating 0.2 mM DIG-dNTPs (Roche) into PCR reactions (primers Table 1, conditions as above). DNA was transferred to positively-charged nylon membranes (Roche) in 0.4M NaOH for 2 hours by capillary action and the blots rinsed in 2xSSC (20xSSC is 3M NaCl, 0.3 M NaCitrate) and UV fixed for 2 minutes. Blots were pre-hybridised for 30 minutes at 42° C with DIG-Easy Hyb solution (Roche) before the addition of 6-10 μL probe followed by hybridisation at 42°C overnight. After hybridisation, the blots were washed and detected with CDP-Star (Roche) according to the manufacturer's instructions. The blots were exposed to Kodak X-ray film for 5 sec, 15 sec, 30 sec, 1 min, 5 min, 20 min and overnight exposures. A reference blot for quantification of band intensity was generated by Southern transfer and detection of 2-fold serial dilutions of omcB positive control PCR product as described above.

DISCUSSION OF EXAMPLES 1 AND 2

A common feature of many chlamydial infections is that they are often asymptomatic and may persist for long periods of time if left untreated. It is likely that this inability of the host to clear the chlamydial infection enables the organism to establish a chronic state, which eventually leads to the resultant adverse immunopathology. What is unknown however, is whether these chronic/persistent chlamydial infections trigger the immune system in such a way as to induce adverse immunopathology. At appropriate concentrations, IFN-δ has been shown to inhibit the growth of *C. trachomatis*, *C. psittaci* and *C. pneumoniae* (see Beatty *et al.*, 1994). The mechanism by which this occurs is

thought to be *via* the induction of host cell indoleamine 2,3-dioxygenase, which results in the depletion of the host cell's tryptophan pool and a resultant nutrient deprivation for the chlamydiae. While the effects of various stress conditions (*e.g.*, direct nutrient starvation, IFN-δ treatment, penicillin treatment) have been well studied in the *C. trachomatis* system, very little has been done with *C. pneumoniae*. The current disclosure is the first to use IFN-δ treatment of *C. pneumoniae* and to demonstrate morphologically abnormal, persistent forms in this species. Very recently, Wolf *et al.* (2000) also reported the induction of abnormal forms of *C. pneumoniae* using ampicillin treatment, with RB morphology similar to that observed in our study using IFN-δ.

It is possible that the persistent phase of the chlamydial developmental cycle might be induced by a range of triggers, each resulting in growth-restricted aberrant chlamydial development. As suggested by Wolf *et al.* (2000) such growth restrictions might be more common *in vivo* than previously thought, making this phase crucial *in vivo*. If such growth-restricted persistent phases do occur regularly, then it might be expected that the organism would have an altered gene expression profile. As a preliminary study, the present inventors selected 14 genes for analysis. The gene transcription analyses were normalised to facilitate an accurate comparison between treatment groups on a gene-by-gene basis. While no obviously down-regulated genes were found, five of the 14 genes were found to be significantly and reproducibly upregulated in IFN-δ-treated cultures.

Two of these genes, *ompA* and *ompB*, are structural proteins thought to be important in cell wall rigidity. Disregulated expression of such proteins might explain the aberrant RB morphology observed in persistent cultures, particularly the multi-membranous forms seen in 48-hour IFN-δ cultures. The enzyme pyruvate kinase (*pyk*) was chosen for analysis because it catalyses the final step in glycolysis, from phosphoenolpyruvate to pyruvate with the release of ATP. The fact that *pyk* was upregulated in IFN-δ-treated cultures might suggest that under stress conditions, *C. pneumoniae* requires the release of stored energy. *Cpn0585* was the most upregulated gene identified and this gene has a homologue, *incA*, in both *C. trachomatis* and *C. psittaci* whose protein product has been localised to the chlamydial inclusion membrane (Bannantine *et al.*, 1998). It is likely that its role is either; (1) to ensure that individual inclusions fuse during chlamydial growth (although *C. pneumoniae* inclusions apparently

do not fuse) or (2) to act as a porin to obtain nutrients from the host cell but presumably also to export key chlamydial proteins into its host cell, thereby influencing the ongoing infection. The gene *incA* is one of three *inc* genes, A, B and C, in the chlamydial genome (Stephens *et al.*, 1999) and has very recently been shown to be required for fusion of *C. trachomatis* inclusions (Suchland *et al.*, 2000). Upregulation of IncA (Cpn0585) in persistent *C. pneumoniae* cultures is, therefore, of particular interest and suggests that this pathogen has mechanisms for modulating its survival when under stressful conditions (IFN-δ-induced persistence; macrophage infection).

The other interesting gene that was upregulated in the persistent phase was *nlpD*. The *C. pneumoniae nlpD* gene product has significant homology with a major extracellular protein family, p60, from organisms such as *Listeria monocytogenes* (Bubert *et al.*, 1992), *Enterococcus faecalis* and *Bacillus* (Margot *et al.*, 1998). In these microorganisms, the protein has two functional domains, an N-terminal domain that contains repeated motifs thought to be responsible for binding to peptidoglycan and a C-terminal domain that has different activities depending on the organism, but usually is associated with key catalytic activities (eg peptidase). In *Listeria*, the homologous gene, *iap* (invasion associated protein) has been shown to be required for adherence to and invasion of nonphagocytic cells (eg fibroblasts) by this pathogen (Bubert *et al.*, 1992). The *C. pneumoniae nlpD* gene product also has similar features to its P60 homologues. It has a 114 amino acid region at its N-terminal end that displays approximately 40% identity to the peptidoglycan-binding motif seen in p60 family proteins. It also has a region at its C-terminal that shows most similarity to the *Enterococcus* amidase. As with the other p60 proteins, it also has a cleavable N-terminal signal sequence. The involvement of *nlpD* in chlamydial pathogenesis is uncertain, however its upregulation in IFN-δ-induced persistence is of particular interest.

Messenger RNA transcript levels were measured, rather than protein levels, making it difficult to directly compare the present results to earlier reports using immunostaining. Nevertheless, it is interesting to note that no significant upregulation of the *hsp60* gene was observed, whereas others have reported increased staining with anti-Hsp60 antibodies in cells from IFN-δ-induced persistent *C. trachomatis* cultures (Beatty *et al.*, 1993a). These same authors also reported a reduced staining of persistent *C.*

trachomatis RBs with anti-MOMP antibodies, whereas the present inventors found a significant upregulation of *ompA* gene transcripts. As observed by Matsumoto & Manire (1970) with penicillin treatment of *C. psittaci* cultures, multi-membraned forms were often present in stressed chlamydial cultures. These multi-membranous structures, which were also observed in the present study, probably contain abnormally formed surface structural proteins. It is possible that while there is some upregulation of *ompA* at the mRNA level, the protein may not be properly folded and or presented at the RB surface. This might explain the abnormal RB morphology that is commonly observed as well as the ineffective anti-MOMP antibody staining reported by Beatty *et al.* (1993a).

It is clear from the present study that *C. pneumoniae* can be induced to produce a proportion of morphologically abnormal persistent forms *in vitro*. These persistent forms have a considerably altered gene transcription profile that might represent a generic stressed state.

EXAMPLE 3

Preparation of antibodies specific to CPn0585 *or* NlpD

Short stretches of amino acids forming suitable peptide immunogens can be selected from a target gene/protein using standard methods or computer algorithms known in the art. For example reference may be made to Pellequer, J.-L., Westhof, E. and van Regenmortel, M. H. V. (1994) Epitope predictions from the primary structure of proteins. In Peptide antigens: a practical approach, pp7-25, Ed. Wisdom, G. B. (Oxford). Several short peptides have been designed for NlpD and CPn0585 as follows:

Two peptides have been designed, which relate to protein AAD18724 corresponding to CPn0585 (SEQ ID NO: 2):

1. A peptide consisting of the N-terminal and C-terminal sequences with a Cys residue between them (the combined N+C peptide) and having the following sequence:

Met-Ala-Thr-Pro-Ala-Gln-Lys-Ser-Cys-Arg-Leu-Glu-Gln-Glu-Gln-Phe-Gln-Gly [SEQ ID NO: 37]

N-Terminus H-; C-Terminus -OH

Length 18; Mass 10 mg

Molecular Wt 2052.3; Hydrophobicity 0.09

Conjugation 5mg; Carrier Diphtheria Toxoid

Linker Maleimidocaproyl-N-Hydroxysuccinimide (MCS)

2. A peptide which was positive in PREDITOP and is both hydrophilic, and has a natural Cys at the C-terminal end of the sequence, which can be used for conjugation purposes, and has the following sequence:

Thr-Val-Gln-Asp-Leu-Arg-Ser-Arg-Ile-Asp-Asp-Glu-Gln-Lys-Arg-Cys [SEQ ID NO: 38]

N-Terminus H-; C-Terminus -NH2

Length 16; Molecular Wt 1961.2

Hydrophobicity -0.14; Charge +1(+5-4)

Conjugation 5mg; Carrier Diphtheria Toxoid

Linker Maleimidocaproyl-N-Hydroxysuccinimide (MCS)

Two peptides have been designed, which relate to protein AAD19040, corresponding to NlpD as follows:

1. A peptide consisting of the combined N-terminal and C-terminal sequences with a Cys residue between them (the combined N+C peptide)

Met-Asn-Arg-Arg-Asp-Met-Val-Cys-Pro-Gly-Asp-Gln-Leu-Arg-Ile-Arg [SEQ ID NO: 39]

N-Terminus H-; C-Terminus -OH

Length 16; Mass 10 mg

Molecular Wt 1960.4; Hydrophobicity 0.07

Conjugation 5mg; Carrier Diphtheria Toxoid

Linker Maleimidocaproyl-N-Hydroxysuccinimide (MCS)

2. The peptide with the highest value from the PREDITOP predictive method, which lacks a natural Cys in the sequence, but to which is added a terminal Cys for conjugation purposes, and has the following sequence:

Val-Thr-Ser-Lys-Arg-Ile-Gly-Val-Lys-Asp-Tyr-Asp-Glu-Gly-Phe-Cys [SEQ ID NO: 40]

N-Terminus H-; C-Terminus -NH2

Length 16; Mass 10 mg

Molecular Wt 1816.1; Hydrophobicity 0.11

Conjugation 5mg; Carrier Diphtheria Toxoid

Linker Maleimidocaproyl-N-Hydroxysuccinimide (MCS)

These peptides will be used to immunise rabbits according to standard methods and antisera or antibodies derived therefrom used to diagnose chronic disease and persistent infection.

The disclosure of every patent, patent application, and publication cited herein is hereby incorporated herein by reference in its entirety.

The citation of any reference herein should not be construed as an admission that such reference is available as "Prior Art" to the instant application

Throughout the specification the aim has been to describe the preferred embodiments of the invention without limiting the invention to any one embodiment or specific collection of features. Those of skill in the art will therefore appreciate that, in light of the instant disclosure, various modifications and changes can be made in the particular embodiments exemplified without departing from the scope of the present invention. All such modifications and changes are intended to be included within the scope of the appended claims.

TABLES

TABLE 1

Primer pairs and PCR product size for the genes under investigation.

Gene	Primers		PCR Product (bp)
16S rRNA	Ct16S-F2	5'-GGA TTT ATT GGG CGT AAA GG [SEQ ID NO: 41]	290
	Ct16S-R	5'-TCC ACA TCA AGT ATG CAT CG [SEQ ID NO: 42]	
OmpA	CpnompA-F	5'-GCTGCAAACTATACTACTGC [SEQ ID NO: 43]	125
	CpnompA-R	5'-GAAAACATCAAAGCGATCCC [SEQ ID NO: 44]	
OmpB	CpnompB-F	5'-GTGATGGGAAATTAGTCTGG [SEQ ID NO: 45]	212
	CpnompB-R	5'-ATC CTG TGT TCA CTA CTT CG [SEQ ID NO: 46]	
OmcB	CpnomcB-F	5'-AGCAGAAGTTTACTCTGTCG [SEQ ID NO: 47]	242
	CpnomcB-R	5'-CTACTGATGGAAACCTAAGC [SEQ ID NO: 48]	
76kDa	Cpn76kDa-F	5'-AAGATATCAAGGCTACTGATGAGGAAACCG [SEQ ID NO: 49]	255
	Cpn76kDa-R	5'-TTGATATCTAGAACTTGCTGCAGCGGGA [SEQ ID NO: 50]	
pmp1	Cpnpmp1-F	5'-GACTACTGCTATAGGTAAGG [SEQ ID NO: 51]	165
	Cpnpmp1-R	5'-GAGATGCTAAGTTTCCTAGC [SEQ ID NO: 52]	
GltX	CpngltX-F	5'-TCTCTTTCGTCCATTGATCG [SEQ ID NO: 53]	125
	CpngltX-R	5'-CTCAGGATTGTTAGAGTACC [SEQ ID NO: 54]	
GroELS	Cpnhsp60B-F	5'-GTCCAGTGAAATCATGGCCG [SEQ ID NO: 55]	298
	Cpnhsp60AI-R	5'-CCCATGTTTTCATGTTTGTC [SEQ ID NO: 56]	

Gene	Primers		PCR Product (bp)
YaeT	CpnyaeT-F	5'-TCAGGAAATCAAGTCGTTCC [SEQ ID NO: 57]	253
	CpnyaeT-R	5'-AGATTCCTGAGAACGTAAGC [SEQ ID NO: 58]	
Pyk	Cpnpyk-F	5'-TGTTGTTGTCTCTTCAGAGG [SEQ ID NO: 59]	152
	Cpnpyk-R	5'-CTACCCCAAACTTAAGATCC [SEQ ID NO: 60]	
NlpD	CpnnlpD-F	5'-TCAATGATCTTACCACCACC [SEQ ID NO: 61]	164
	CpnnlpD-R	5'-GTTACGCAATGCTATTGTCC [SEQ ID NO: 62]	
Cpn0585	Cpn0585-F	5'-TGCATCTTATCAAGAGCTCG [SEQ ID NO: 63]	267
	Cpn0585-R	5'-GAAGTTAGCGGATTTAGAGG [SEQ ID NO: 64]	
Cpn1046	Cpn1046-F	5'-GAGGAGAACTGATAAGAACG [SEQ ID NO: 65]	269
	Cpn1046-R	5'-CTTAACTCCTGATCTCATCC [SEQ ID NO: 66]	

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CLAIMS

1. A method for detecting an organism of the Chlamydiaceae family in the persistent phase of its developmental cycle, said method comprising detecting, relative to the lytic phase of said developmental cycle, a change in the level and/or functional activity of an expression product of a gene selected from *pyk*, *nlpD*, *Cpn0585*, or a gene belonging to the same regulatory or biosynthetic pathway as *pyk*, *nlpD*, *Cpn0585*, *ompA*, *ompB*, *hsp60* or as a gene involved in the biosynthesis of LPS, or a variant of said gene.

2. The method of claim 1, wherein said change is an at least 10% change in said level and/or functional activity.

3. The method of claim 1, wherein said gene is selected from *pyk*, *nlpD*, *Cpn0585* or a gene belonging to the same regulatory or biosynthetic pathway as *pyk*, *nlpD* or *Cpn0585*, or a variant of said gene.

4. The method of claim 3, wherein the gene belonging to the same regulatory or biosynthetic pathway as *pyk* is selected from *mrsA*, *pfkA_1*, *pfkA_2*, *dhnA*, *gapA*, *pgk*, *eno*, *pgmA*, *pgm*, *pgi*, or *tpiS*.

5. The method of claim 3, wherein the gene belonging to the same regulatory or biosynthetic pathway as *nlpD* is selected from *amiA*, *murE*, *pbp3*, *yabC*, *murA*, *dacF*, *pbpB*, *amiB*, *glmU*, *murF*, *mraY*, *murD*, *murG*, *murC*, *ddlA*, *glmS* or *murB*.

6. The method of claim 3, wherein the gene belonging to the same regulatory or biosynthetic pathway as *Cpn0585* is selected from *incA*, *incB*, *incC* or *Cpn0186*.

7. The method of claim 1, wherein said gene is selected from *pyk*, *nlpD*, *Cpn0585* or variant thereof.

8. The method of claim 7, wherein *pyk* comprises the sequence set forth in SEQ ID NO: 9, 17, 21 or 31, or variant thereof.

9. The method of claim 7, wherein the expression product of *pyk* is a transcript encoded by the sequence set forth in SEQ ID NO: 9, 17, 21 or 31, or variant thereof.

10. The method of claim 8, wherein the expression product of *pyk* is a polypeptide comprising the sequence set forth in SEQ ID NO: 10, 18, 22 or 32, or variant thereof.

11. The method of claim 7, wherein *nlpD* comprises the sequence set forth in SEQ ID NO: 3, 15, 25 or 35, or variant thereof.

12. The method of claim 11, wherein the expression product of *nlpD* is a transcript encoded by the sequence set forth in SEQ ID NO: 3, 15, 25 or 35, or variant thereof.

13. The method of claim 11, wherein the expression product of *nlpD* is a polypeptide comprising the sequence set forth in SEQ ID NO: 4, 16, 26 or 36, or variant thereof.

14. The method of claim 7, wherein *Cpn0585* comprises the sequence set forth in SEQ ID NO: 1 or 33.

15. The method of claim 14, wherein the expression product of *Cpn0585* is a transcript encoded by the sequence set forth in SEQ ID NO: 1 or 33, or variant thereof.

16. The method of claim 14, wherein the expression product of *Cpn0585* is a polypeptide comprising the sequence set forth in SEQ ID NO: 2 or 34, or variant thereof.

17. The method of claim 1, wherein said genes involved in the biosynthesis of LPS are selected from *gseA*, *kdsB*, *lpxD*, *lpxA*, *lpxC*, *kdsA* or *lpxB*.

18. A method for diagnosis of a persistent or chronic infection in a patient, wherein said infection is caused by an organism of the Chlamydiaceae family, said method comprising detecting in a biological sample obtained from said patient, relative to the lytic phase of the developmental cycle of said organism, a change in the level and/or functional activity of an expression product of a gene selected from *pyk*, *nlpD*, *Cpn0585*, or a gene belonging to the same regulatory or biosynthetic pathway as *pyk*, *nlpD*, *Cpn0585*, *ompA*, *ompB*, *hsp60* or as a gene involved in the biosynthesis of LPS, or a variant of said gene.

19. The method of claim 18, wherein said change is an at least 10% change in said level and/or functional activity.

20. The method of claim 18, wherein said gene is selected from *pyk*, *nlpD*, *Cpn0585* or a gene belonging to the same regulatory or biosynthetic pathway as *pyk*, *nlpD* or *Cpn0585*, or a variant of said gene.

21. The method of claim 20, wherein the gene belonging to the same regulatory or biosynthetic pathway as *pyk* is selected from *mrsA*, *pfkA_1*, *pfkA_2*, *dhnA*, *gapA*, *pgk*, *eno*, *pgmA*, *pgm*, *pgi*, or *tpiS*.

22. The method of claim 20, wherein the gene belonging to the same regulatory or biosynthetic pathway as *nlpD* is selected from *amiA*, *murE*, *pbp3*, *yabC*, *murA*, *dacF*, *pbpB*, *amiB*, *glmU*, *murF*, *mraY*, *murD*, *murG*, *murC*, *ddlA*, *glmS* or *murB*.

23. The method of claim 20, wherein the gene belonging to the same regulatory or biosynthetic pathway as *Cpn0585* is selected from *incA*, *incB*, *incC* or *Cpn0186*.

24. The method of claim 18, wherein said gene is selected from *pyk*, *nlpD*, *Cpn0585* or variant thereof.

25. The method of claim 24, wherein *pyk* comprises the sequence set forth in SEQ ID NO: 9, 17, 21 or 31, or variant thereof.

26. The method of claim 25, wherein the expression product of *pyk* is a transcript encoded by the sequence set forth in SEQ ID NO: 9, 17, 21 or 31, or variant thereof.

27. The method of claim 25, wherein the expression product of *pyk* is a polypeptide comprising the sequence set forth in SEQ ID NO: 10, 18, 22 or 32, or variant thereof.

28. The method of claim 24, wherein *nlpD* comprises the sequence set forth in SEQ ID NO: 3, 15, 25 or 35, or variant thereof.

29. The method of claim 28, wherein the expression product of *nlpD* is a transcript encoded by the sequence set forth in SEQ ID NO: 3, 15, 25 or 35, or variant thereof.

30. The method of claim 28, wherein the expression product of *nlpD* is a polypeptide comprising the sequence set forth in SEQ ID NO: 4, 16, 26 or 36, or variant thereof.

31. The method of claim 24, wherein *Cpn0585* comprises the sequence set forth in SEQ ID NO: 1 or 33.

32. The method of claim 31, wherein the expression product of *Cpn0585* is a transcript encoded by the sequence set forth in SEQ ID NO: 1 or 33, or variant thereof.

33. The method of claim 31, wherein the expression product of *Cpn0585* is a polypeptide comprising the sequence set forth in SEQ ID NO: 2 or 34, or variant thereof.

34. The method of claim 18, wherein said genes involved in the biosynthesis of LPS are selected from *gseA*, *kdsB*, *lpxD*, *lpxA*, *lpxC*, *kdsA* or *lpxB*.

35. The method of claim 18, further comprising:

– contacting the biological sample with an antigen-binding molecule that is immuno-interactive with a polypeptide expressed from said gene;

– measuring the concentration of a complex comprising said polypeptide and the antigen binding molecule in said contacted sample; and

– relating said measured complex concentration to the concentration of said polypeptide in said sample.

36. The method of claim 36, wherein the concentration of said polypeptide in said biological sample is compared to a reference level of said polypeptide corresponding to said lytic phase.

The method of claim 18, further comprising:

– measuring the level of a transcript expressed from said gene in said biological sample.

37. The method of claim 36, wherein the level of said transcript in said biological sample is compared to a reference level of said transcript corresponding to said lytic phase.

38. The method of claim 18, further comprising:

– contacting the biological sample with an antigen corresponding to at least a portion of a polypeptide encoded by said gene;

– measuring the concentration of a complex comprising said antigen and an antigen-binding molecule in said contacted sample; and

– relating said measured complex concentration to the concentration of antigen-binding molecule in said sample to thereby determine the amount or level of said polypeptide in said sample.

39. The method of claim 38, wherein the concentration of said antigen-binding molecule in said biological sample is compared to a reference level of said antigen-binding molecule corresponding to said lytic phase.

40. The method of claim 18, further comprising

– contacting the biological sample with an antigen corresponding to at least a portion of a polypeptide encoded by said gene;

– measuring the level of antigen-specific T cell proliferation in said contacted sample to thereby determine the amount or level of said polypeptide in said sample.

41. The method of claim 40, wherein the level of said antigen-specifc T cell proliferation in said biological sample is compared to a reference level of antigen-specifc T cell proliferation corresponding to said lytic phase.

42. A method of screening for an agent that modulates the expression of a gene or the level and/or functional activity of an expression product of said gene, wherein said gene is selected from *pyk*, *nlpD*, *Cpn0585*, or a gene belonging to the same regulatory or biosynthetic pathway as *pyk*, *nlpD*, *Cpn0585*, *ompA*, *ompB*, *hsp60* or as a gene involved in the biosynthesis of LPS, or a variant of said gene, said method comprising:

– contacting a preparation comprising a polypeptide encoded by said gene, or biologically active fragment of said polypeptide, or variant or derivative of these, or a genetic sequence that modulates the expression of said gene, with a test agent; and

– detecting a change in the level and/or functional activity of said polypeptide or biologically active fragment thereof, or variant or derivative, or of a product expressed from said genetic sequence.

43. The method of claim 42, wherein said gene is selected from *pyk*, *nlpD*, *Cpn0585* or variant thereof.

44. The method of claim 43, wherein the polypeptide encoded by *pyk* comprises the sequence set forth in SEQ ID NO: 10, 18, 22 or 32, or variant thereof.

45. The method of claim 43, wherein the polypeptide encoded by *nlpD* comprises the sequence set forth in SEQ ID NO: 4, 16, 26 or 36, or variant thereof.

46. The method of claim 43, wherein the polypeptide encoded by *Cpn0585* comprises the sequence set forth in SEQ ID NO: 2 or 34, or variant thereof.

47. The method of claim 42, wherein the agent reduces, abrogates or otherwise impairs the expression of *pyk*, *nlpD*, *Cpn0585*, *ompA*, *ompB*, *hsp60* or a gene involved in the biosynthesis of LPS, or the level and/or functional activity of an expression product of these genes.

48. The method of claim 42, wherein the agent increases, enhances or otherwise elevates the expression of a gene or the level and/or functional activity of an expression product of said gene, which reduces, abrogates or otherwise impairs the expression of *pyk*, *nlpD*, *Cpn0585*, *ompA*, *ompB*, *hsp60* or a gene involved in the biosynthesis of LPS or the level and/or functional activity of an expression product of *pyk*, *nlpD*, *Cpn0585*, *ompA*, *ompB*, *hsp60* or said gene involved in the biosynthesis of LPS.

49. The method of claim 43, wherein the agent reduces, abrogates or otherwise impairs the expression of *pyk*, *nlpD* or *Cpn0585* or the level and/or functional activity of an expression product of these genes.

50. The method of claim 43, wherein the agent increases, enhances or otherwise elevates the expression of a gene or the level and/or functional activity of an expression product of said gene, which reduces, abrogates or otherwise impairs the expression of *pyk*, *nlpD* or *Cpn0585*, or the level and/or functional activity of an expression product of *pyk*, *nlpD* or *Cpn0585*.

51. A composition for treatment and/or prophylaxis of chronic infection caused by an organism of the Chlamydiaceae family, comprising an agent that modulates the expression of a gene or the level and/or functional activity of an expression product of said gene, wherein said gene is selected from *pyk*, *nlpD*, *Cpn0585*, or a gene belonging to the same regulatory or biosynthetic pathway as *pyk*, *nlpD*, *Cpn0585*, *ompA*, *ompB*, *hsp60* or as a gene involved in the biosynthesis of LPS, or a variant of said gene, together with a pharmaceutically acceptable carrier and/or diluent.

52. The composition of claim 51, wherein said gene is selected from *pyk*, *nlpD*, *Cpn0585* or variant thereof.

53. The composition of claim 52, wherein the polypeptide encoded by *pyk* comprises the sequence set forth in SEQ ID NO: 10, 18, 22 or 32, or variant thereof.

54. The composition of claim 52, wherein the polypeptide encoded by *nlpD* comprises the sequence set forth in SEQ ID NO: 4, 16, 26 or 36, or variant thereof.

55. The composition of claim 52, wherein the polypeptide encoded by *Cpn0585* comprises the sequence set forth in SEQ ID NO: 2 or 34, or variant thereof.

56. The composition of claim 51, wherein the agent reduces, abrogates or otherwise impairs the expression of *pyk*, *nlpD*, *Cpn0585*, *ompA*, *ompB*, *hsp60* or a gene involved in the biosynthesis of LPS, or the level and/or functional activity of an expression product of these genes.

57. The composition of claim 51, wherein the agent increases, enhances or otherwise elevates the expression of a gene or the level and/or functional activity of an expression product of said gene, which reduces, abrogates or otherwise impairs the expression of *pyk*, *nlpD*, *Cpn0585*, *ompA*, *ompB*, *hsp60* or a gene involved in the biosynthesis of LPS, or the level and/or functional activity of an expression product of *pyk*, *nlpD*, *Cpn0585*, *ompA*, *ompB*, *hsp60* or said gene involved in the biosynthesis of LPS.

58. The composition of claim 52, wherein the agent reduces, abrogates or otherwise impairs the expression of *pyk*, *nlpD* or *Cpn0585* or the level and/or functional activity of an expression product of these genes.

59. The composition of claim 52, wherein the agent increases, enhances or otherwise elevates the expression of a gene or the level and/or functional activity of an expression product of said gene, which reduces, abrogates or otherwise impairs the expression of *pyk*, *nlpD* or *Cpn0585*, or the level and/or functional activity of an expression product of *pyk*, *nlpD* or *Cpn0585*.

60. A method of modulating the expression of a gene or the level and/or functional activity of an expression product of said gene, wherein said gene is selected from *pyk*, *nlpD*, *Cpn0585*, or a gene belonging to the same regulatory or biosynthetic pathway as *pyk*, *nlpD*, *Cpn0585*, *ompA*, *ompB*, *hsp60* or as a gene involved in the biosynthesis of LPS, or a variant of said gene, said method comprising contacting a cell containing said gene with an agent for a time and under conditions sufficient to modulate the expression of said gene or the level and/or functional activity of said expression product.

61. The method of claim 60, wherein said gene is selected from *pyk*, *nlpD*, *Cpn0585* or variant thereof.

62. The method of claim 61, wherein the polypeptide encoded by *pyk* comprises the sequence set forth in SEQ ID NO: 10, 18, 22 or 32, or variant thereof.

63. The method of claim 61, wherein the polypeptide encoded by *nlpD* comprises the sequence set forth in SEQ ID NO: 4, 16, 26 or 36, or variant thereof.

64. The method of claim 61, wherein the polypeptide encoded by *Cpn0585* comprises the sequence set forth in SEQ ID NO: 2 or 34, or variant thereof.

65. The method of claim 60, wherein the agent reduces, abrogates or otherwise impairs the expression of *pyk*, *nlpD*, *Cpn0585*, *ompA*, *ompB*, *hsp60* or a gene involved in the biosynthesis of LPS, or the level and/or functional activity of an expression product of these genes.

66. The method of claim 60, wherein the agent increases, enhances or otherwise elevates the expression of a gene or the level and/or functional activity of an expression product of said gene, which reduces, abrogates or otherwise impairs the expression of *pyk*, *nlpD*, *Cpn0585*, *ompA*, *ompB*, *hsp60* or a gene involved in the biosynthesis of LPS, or the level and/or functional activity of an expression product of *pyk*, *nlpD*, *Cpn0585*, *ompA*, *ompB*, *hsp60* or said gene involved in the biosynthesis of LPS.

67. The method of claim 61, wherein the agent reduces, abrogates or otherwise impairs the expression of *pyk*, *nlpD* or *Cpn0585* or the level and/or functional activity of an expression product of these genes.

68. The method of claim 61, wherein the agent increases, enhances or otherwise elevates the expression of a gene or the level and/or functional activity of an expression product of said gene, which reduces, abrogates or otherwise impairs the expression of *pyk*, *nlpD* or *Cpn0585*, or the level and/or functional activity of an expression product of *pyk*, *nlpD* or *Cpn0585*.

69. The method of claim 60, wherein the cell is an epithelial cell.

70. The method of claim 69, wherein the epithelial cell is from the genital tract, respiratory tract, cardiovascular system, reproductive system or conjunctiva.

71. The method of claim 60, wherein the cell is a macrophage.

72. The method of claim 60, wherein the cell is associated with atherosclerotic tissue.

73. The method of claim 60, wherein the cell is associated with multiple sclerosis brain tissue.

74. A method for treatment and/or prophylaxis of a chronic infection caused by an organism of the Chlamydiaceae family in a patient, said method comprising administering to said patient an effective amount of an agent that modulates the expression of a gene or the level and/or functional activity of an expression product of said gene, wherein said gene is selected from *pyk*, *nlpD*, *Cpn0585*, or a gene belonging to the same regulatory or biosynthetic pathway as *pyk*, *nlpD*, *Cpn0585*, *ompA*, *ompB*, *hsp60* or as a gene involved in

the biosynthesis of LPS, or a variant of said gene for a time and under conditions sufficient to treat and/or prevent said infection.

75. The method of claim 74, wherein said gene is selected from *pyk*, *nlpD*, *Cpn0585* or variant thereof.

76. The method of claim 75, wherein the polypeptide encoded by *pyk* comprises the sequence set forth in SEQ ID NO: 10, 18, 22 or 32, or variant thereof.

77. The method of claim 75, wherein the polypeptide encoded by *nlpD* comprises the sequence set forth in SEQ ID NO: 4, 16, 26 or 36, or variant thereof.

78. The method of claim 75, wherein the polypeptide encoded by *Cpn0585* comprises the sequence set forth in SEQ ID NO: 2 or 34, or variant thereof.

79. The method of claim 74, wherein the agent reduces, abrogates or otherwise impairs the expression of *pyk*, *nlpD*, *Cpn0585*, *ompA*, *ompB*, *hsp60* or a gene involved in the biosynthesis of LPS, or the level and/or functional activity of an expression product of these genes.

80. The method of claim 74, wherein the agent increases, enhances or otherwise elevates the expression of a gene or the level and/or functional activity of an expression product of said gene, which reduces, abrogates or otherwise impairs the expression of *pyk*, *nlpD*, *Cpn0585*, *ompA*, *ompB*, *hsp60* or a gene involved in the biosynthesis of LPS, or the level and/or functional activity of an expression product of *pyk*, *nlpD*, *Cpn0585*, *ompA*, *ompB*, *hsp60* or said gene involved in the biosynthesis of LPS.

81. The method of claim 75, wherein the agent reduces, abrogates or otherwise impairs the expression of *pyk*, *nlpD* or *Cpn0585* or the level and/or functional activity of an expression product of these genes.

82. The method of claim 75, wherein the agent increases, enhances or otherwise elevates the expression of a gene or the level and/or functional activity of an expression product of said gene, which reduces, abrogates or otherwise impairs the expression of *pyk*, *nlpD* or

Cpn0585, or the level and/or functional activity of an expression product of *pyk*, *nlpD* or *Cpn0585*.

83. A method for treatment and/or prophylaxis of a lytic or chronic infection caused by an organism of the Chlamydiaceae family in a patient, said method comprising sequentially or simultaneously administering to said patient effective amounts of a first agent and a second agent for a time and under conditions sufficient to treat and/or prevent said infection, wherein said first agent modulates the expression of a first gene expressed in the persistent phase of the developmental cycle of said organism or the level and/or functional activity of an expression product of said first gene, and wherein said second agent modulates the expression of a second gene expressed in the lytic phase of said developmental cycle or the level and/or functional activity of an expression product of said second gene.

84. The method of claim 83, wherein said first gene is selected from *pyk*, *nlpD*, *Cpn0585*, *ompA*, *ompB*, *hsp60* or a gene involved in the biosynthesis of LPS, or a gene belonging to the same regulatory or biosynthetic pathway as *pyk*, *nlpD*, *Cpn0585*, *ompA*, *ompB*, *hsp60* or said gene involved in the biosynthesis of LPS, or a variant of these.

85. The method of claim 83, wherein said first gene is selected from *pyk*, *nlpD* or *Cpn0585*, or a gene belonging to the same regulatory or biosynthetic pathway as *pyk*, *nlpD* or *Cpn0585*.

86. The method of claim 84, wherein said first agent reduces, abrogates or otherwise impairs the expression of *pyk*, *nlpD*, *Cpn0585*, *ompA*, *ompB*, *hsp60* or a gene involved in the biosynthesis of LPS, or the level and/or functional activity of an expression product of these genes.

87. The method of claim 84, wherein said first agent increases, enhances or otherwise elevates the expression of a gene or the level and/or functional activity of an expression product of said gene, which reduces, abrogates or otherwise impairs the expression of *pyk*, *nlpD*, *Cpn0585*, *ompA*, *ompB* or *hsp60* or a gene involved in the biosynthesis of LPS, or the level and/or functional activity of an expression product of *pyk*, *nlpD*, *Cpn0585*, *ompA*, *ompB*, *hsp60* or said gene involved in the biosynthesis of LPS.

88. The method of claim 85, wherein the agent reduces, abrogates or otherwise impairs the expression of *pyk*, *nlpD* or *Cpn0585* or the level and/or functional activity of an expression product of these genes.

89. The method of claim 85, wherein the agent increases, enhances or otherwise elevates the expression of a gene or the level and/or functional activity of an expression product of said gene, which reduces, abrogates or otherwise impairs the expression of *pyk*, *nlpD* or *Cpn0585*, or the level and/or functional activity of an expression product of *pyk*, *nlpD* or *Cpn0585*.

90. The method of claim 83, wherein said second agent is an antibiotic effective in treating and/or preventing said lytic infection.

91. The method of claim 83, wherein second agent is immuno-interactive with an antigen expressed in the lytic phase of said developmental cycle.

92. A method for treatment and/or prophylaxis of a lytic or chronic infection caused by an organism of the Chlamydiaceae family in a patient, said method comprising sequentially or simultaneously administering to said patient an effective amount of a first agent that modulates the expression of a first gene expressed in the persistent phase of the developmental cycle of said organism, or the level and/or functional activity of an expression product of said first gene, for a time and under conditions sufficient to cause said organism to enter the lytic phase of said developmental cycle, together with an effective amount of a second agent that modulates the expression of a second gene associated with the lytic phase of said developmental cycle or the level and/or functional activity of an expression product of said second gene, for a time and under conditions sufficient to kill, attenuate or otherwise inactivate said organism.

93. The method of claim 92, wherein said first gene is selected from *pyk*, *nlpD*, *Cpn0585*, *ompA*, *ompB*, *hsp60* or a gene involved in the biosynthesis of LPS, or a gene belonging to the same regulatory or biosynthetic pathway as *pyk*, *nlpD*, *Cpn0585*, *ompA*, *ompB*, *hsp60* or said gene involved in the biosynthesis of LPS, or a variant of these.

94. The method of claim 92, wherein said first gene is selected from *pyk*, *nlpD* or *Cpn0585*, or a gene belonging to the same regulatory or biosynthetic pathway as *pyk*, *nlpD* or *Cpn0585*.

95. The method of claim 93, wherein said first agent reduces, abrogates or otherwise impairs the expression of *pyk*, *nlpD*, *Cpn0585*, *ompA*, *ompB*, *hsp60* or a gene involved in the biosynthesis of LPS, or the level and/or functional activity of an expression product of these genes.

96. The method of claim 93, wherein said first agent increases, enhances or otherwise elevates the expression of a gene or the level and/or functional activity of an expression product of said gene, which reduces, abrogates or otherwise impairs the expression of *pyk*, *nlpD*, *Cpn0585*, *ompA*, *ompB* or *hsp60* or a gene involved in the biosynthesis of LPS, or the level and/or functional activity of an expression product of *pyk*, *nlpD*, *Cpn0585*, *ompA*, *ompB*, *hsp60* or said gene involved in the biosynthesis of LPS.

97. The method of claim 94, wherein the agent reduces, abrogates or otherwise impairs the expression of *pyk*, *nlpD* or *Cpn0585* or the level and/or functional activity of an expression product of these genes.

98. The method of claim 94, wherein the agent increases, enhances or otherwise elevates the expression of a gene or the level and/or functional activity of an expression product of said gene, which reduces, abrogates or otherwise impairs the expression of *pyk*, *nlpD* or *Cpn0585*, or the level and/or functional activity of an expression product of *pyk*, *nlpD* or *Cpn0585*.

99. The method of claim 92, wherein said second agent is an antibiotic effective in treating and/or preventing said lytic infection.

100. The method of claim 92, wherein second agent is immuno-interactive with an antigen expressed in the lytic phase of said developmental cycle.

101. A method for treatment and/or prophylaxis of a lytic or chronic infection caused by an organism of the Chlamydiaceae family in a patient, said method comprising

sequentially or simultaneously administering to said patient effective amounts of a first immunopotentiating agent and a second immunopotentiating agent for a time and under conditions sufficient to treat and/or prevent said infection, said first immunopotentiating agent being selected from a first proteinaceous molecule comprising at least a portion of a polypeptide, or variant or derivative thereof, associated with the persistent phase of the developmental cycle of said organism, or a polynucleotide from which said first proteinaceous molecule is expressed, said second immunopotentiating agent being selected from a second proteinaceous molecule comprising at least a portion of a polypeptide, or a variant or derivative thereof, associated with the lytic phase of said developmental cycle, or a polynucleotide from which said second proteinaceous molecule is expressed.

102. The method of claim 101, wherein the polypeptide of said first proteinaceous molecule is selected from Pyk, NlpD, CPn0585, OmpA, OmpB or Hsp60 or a polypeptide involved in the biosynthesis of LPS, or biologically active fragment thereof, or variant or derivative of these.

103. The method of claim 101, wherein the polypeptide of said first proteinaceous molecule is selected from Pyk, NlpD or CPn0585, or biologically active fragment thereof, or variant or derivative of these.

104. The method of claim 101, wherein the polypeptide of said second proteinaceous molecule is MOMP, or biologically active fragment thereof, or variant or derivative of these.

105. A method for treatment and/or prophylaxis of a lytic or chronic infection caused by an organism of the Chlamydiaceae family in a patient, said method comprising sequentially or simultaneously administering to said patient effective amounts of a first antigen associated with the persistent phase of the developmental cycle of said organism, and a second associated with the lytic phase of said developmental cycle.

106. The method of claim 105, wherein the first antigen comprises at least a portion of a polypeptide selected from Pyk, NlpD, CPn0585, OmpA, OmpB or Hsp60 or a polypeptide

involved in the biosynthesis of LPS, or biologically active fragment thereof, or variant or derivative of these.

107. The method of claim 105, wherein the first antigen comprises at least a portion of a polypeptide selected from Pyk, NlpD or CPn0585, or biologically active fragment thereof, or variant or derivative of these.

108. The method of claim 105, wherein the second antigen comprises at least a portion of MOMP, or biologically active fragment thereof, or variant or derivative of these.

109. An immunopotentiating composition for use in treating or preventing a chronic infection caused by an organism of the Chlamydiaceae family, comprising an antigen associated with the persistent phase of the developmental cycle of said organism, together with a pharmaceutically acceptable carrier and/or diluent.

110. The composition of claim 109, wherein said antigen comprises at least a portion of a polypeptide selected from Pyk, NlpD, CPn0585, OmpA, OmpB or Hsp60 or a polypeptide involved in the biosynthesis of LPS, or biologically active fragment thereof, or variant or derivative of these.

111. The composition of claim 109, wherein said antigen comprises at least a portion of a polypeptide selected from Pyk, NlpD or CPn0585, or biologically active fragment thereof, or variant or derivative of these.

112. The composition of claim 109, further comprising an adjuvant.

113. The composition of claim 112, wherein the adjuvant is a mucosal adjuvant.

114. The composition of claim 109, further comprising at least one additional antigen.

115. The composition of claim 114, wherein the additional antigen(s) are selected from other antigens associated with the persistent phase of said developmental cycle or from of antigens associated with the lytic phase of said developmental cycle.

116. An immunopotentiating composition for use in treating or preventing a chronic infection caused by an organism of the Chlamydiaceae family, comprising a first antigen

associated with the persistent phase of the developmental cycle of said organism and a second antigen associated with the lytic phase of said developmental cycle, together with a pharmaceutically acceptable carrier and/or diluent.

117. The composition of claim 116, wherein the first antigen comprises at least a portion of a polypeptide selected from Pyk, NlpD, CPn0585, OmpA, OmpB or Hsp60 or a polypeptide involved in the biosynthesis of LPS, or biologically active fragment thereof, or variant or derivative of these.

118. The composition of claim 116, wherein the first antigen comprises at least a portion of a polypeptide selected from Pyk, NlpD or CPn0585, or biologically active fragment thereof, or variant or derivative of these.

119. The composition of claim 116, wherein the second antigen comprises at least a portion of MOMP, or biologically active fragment thereof, or variant or derivative of these.

120. The composition of claim 116, further comprising an adjuvant.

121. The composition of claim 120, wherein the adjuvant is a mucosal adjuvant.

122. The composition of claim 116, further comprising at least one additional antigen.

123. The composition of claim 122, wherein the additional antigen(s) are selected from other antigens associated with the persistent phase of said developmental cycle or from of antigens associated with the lytic phase of said developmental cycle.

124. Use of at least one antigen associated with the persistent phase of the developmental cycle of an organism of the Chlamydiaceae family in the manufacture of a medicament for treating and/or preventing chronic chlamydial infection in a patient.

125. Use of at least one antigen associated with the persistent phase of the developmental cycle of an organism of the Chlamydiaceae family together with at least one antigen associated with the lytic phase of said developmental cycle in the manufacture of a medicament for treating and/or preventing chlamydial infection in a patient.

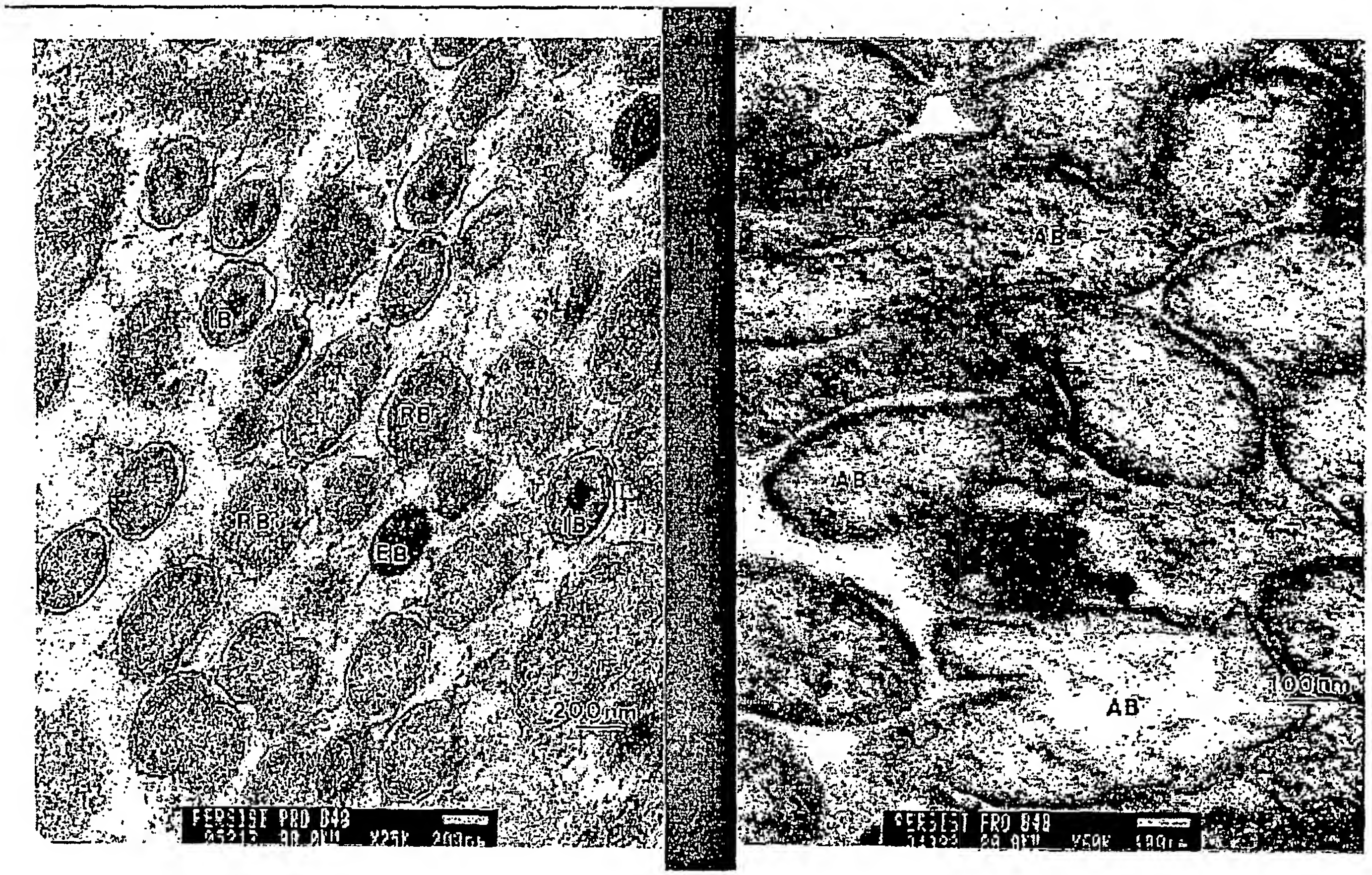
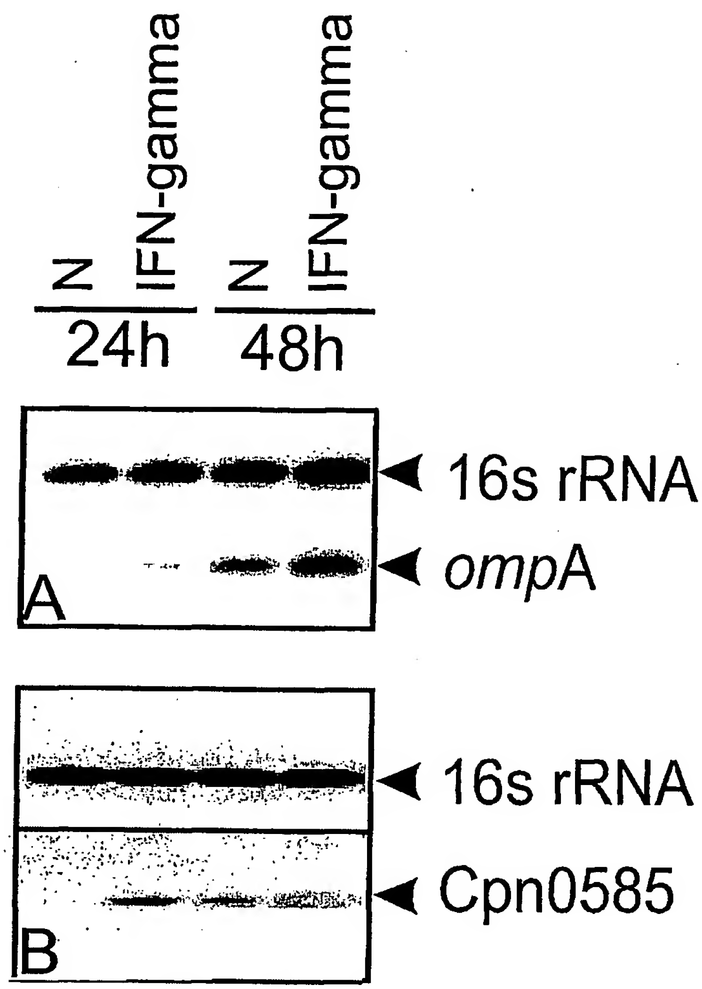


FIGURE 1



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IFN-gamma
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48h
16s rRNA
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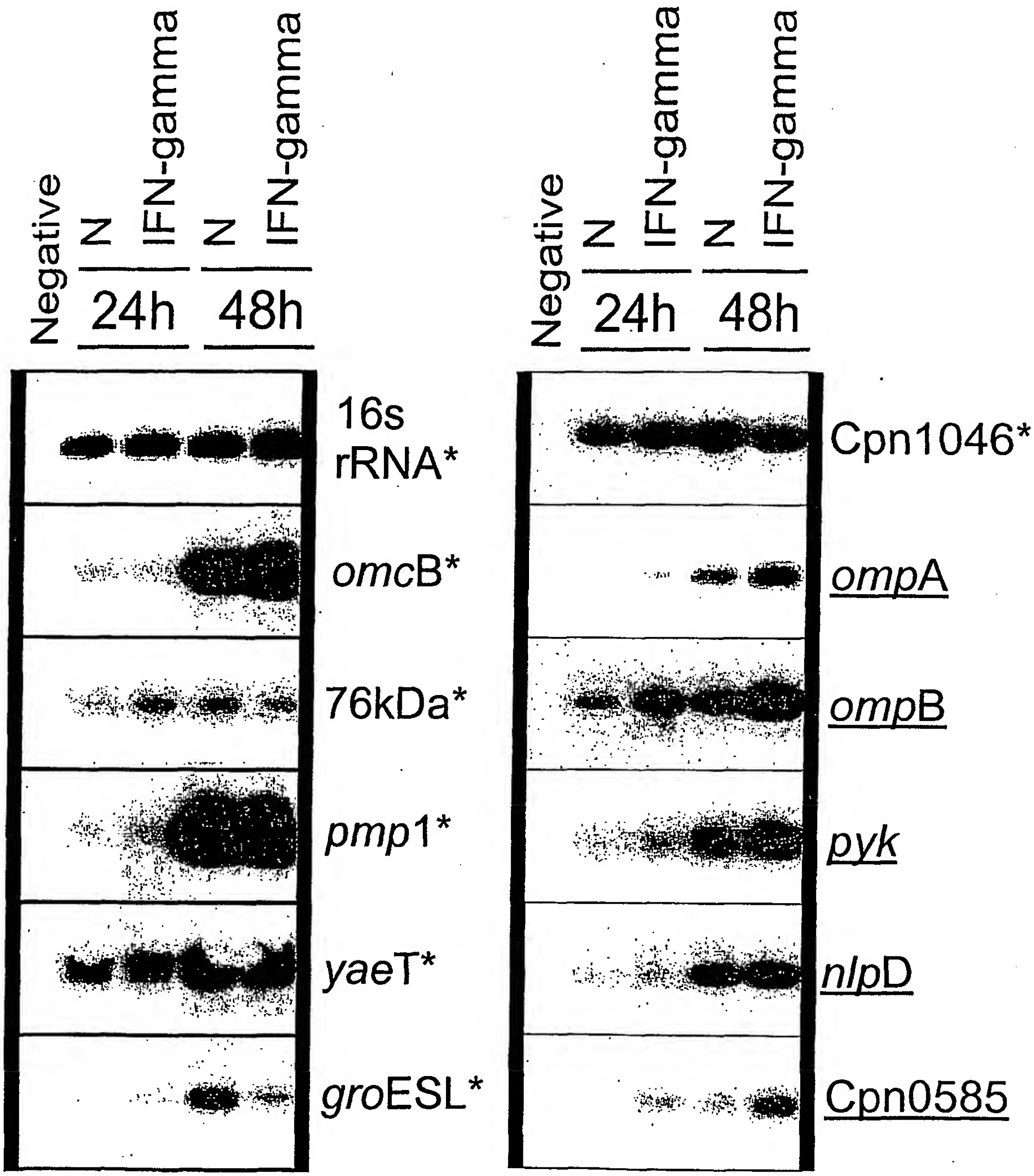
A
16s rRNA
Cpn0585
B

FIGURE 2



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IFN-gamma
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pmp1*
yaeT*
groESL*
Negative
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24h
48h
Cpn1046*
ompA
ompB
pyk
nlpD
Cpn0585

FIGURE 3

SEQUENCE LISTING

<110> Queensland University of Technology (all States other than U.S.)
Mathews, Sarah (U.S. only)
Timms, Peter (U.S. only)

<120> Novel Diagnostic Agents and Uses Therefor

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<150> AU PQ9540/00
<151> 2000-08-18

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taa 2019

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305 310 315 320

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Asn Val Ser Leu Ser Asn Gly Val Val Glu Leu Tyr Thr Asp Thr Ser
            180   185   190

Phe Ser Trp Ser Val Gly Ala Arg Gly Ala Leu Trp Glu Cys Gly Cys

195 200 205

Ala Thr Leu Gly Ala Glu Phe Gln Tyr Ala Gln Ser Lys Pro Lys Val
210 215 220

Glu Glu Leu Asn Val Ile Cys Asn Val Ser Gln Phe Ser Val Asn Lys
225 230 235 240

Pro Lys Gly Tyr Lys Gly Val Ala Phe Pro Leu Pro Thr Asp Ala Gly
245 250 255

Val Ala Thr Ala Thr Gly Thr Lys Ser Ala Thr Ile Asn Tyr His Glu
260 265 270

Trp Gln Val Gly Ala Ser Leu Ser Tyr Arg Leu Asn Ser Leu Val Pro
275 280 285

Tyr Ile Gly Val Gln Trp Ser Arg Ala Thr Phe Asp Ala Asp Asn Ile
290 295 300

Arg Ile Ala Gln Pro Lys Leu Pro Thr Ala Val Leu Asn Leu Thr Ala
305 310 315 320

Trp Asn Pro Ser Leu Leu Gly Asn Ala Thr Ala Leu Ser Thr Thr Asp
325 330 335

Ser Phe Ser Asp Phe Met Gln Ile Val Ser Cys Gln Ile Asn Lys Phe
340 345 350

Lys Ser Arg Lys Ala Cys Gly Val Thr Val Gly Ala Thr Leu Val Asp
355 360 365

Ala Asp Lys Trp Ser Leu Thr Ala Glu Ala Arg Leu Ile Asn Glu Arg
370 375 380

Ala Ala His Val Ser Gly Gln Phe Arg Phe
385 390

<210> 7
<211> 1047
<212> DNA
<213> Chlamydia pneumoniae

<220>
<221> CDS

<222> (1)..(1047)
<223>

<400> 7
ggc ccc ttt gac atg aat agc aag atg cta aaa cat tta cgt tta gca 48
Gly Pro Phe Asp Met Asn Ser Lys Met Leu Lys His Leu Arg Leu Ala
1 5 10 15

acc ctt tcc ttc tct atg ttc ttc ggg att gta tct tct ccc gca gta 96
Thr Leu Ser Phe Ser Met Phe Phe Gly Ile Val Ser Ser Pro Ala Val
20 25 30

tat gcc cta ggg gct gga aac cct gca gct cca gta ctc cca ggt gtg 144
Tyr Ala Leu Gly Ala Gly Asn Pro Ala Ala Pro Val Leu Pro Gly Val
35 40 45

aat cct gag caa acg gga tgg tgt gcc ttc caa ctt tgt aat agt tac 192
Asn Pro Glu Gln Thr Gly Trp Cys Ala Phe Gln Leu Cys Asn Ser Tyr
50 55 60

gat ctt ttt gct gct ctt gca gga agc ctc aaa ttt ggg ttc tat gga 240
Asp Leu Phe Ala Ala Leu Ala Gly Ser Leu Lys Phe Gly Phe Tyr Gly
65 70 75 80

gat tat gtc ttc tca gaa agt gcc cat att acc aat gtc cct gtc att 288
Asp Tyr Val Phe Ser Glu Ser Ala His Ile Thr Asn Val Pro Val Ile
85 90 95

acc tcc gtt acg act tca ggc aca gga aca acg cca acc att acc tct 336
Thr Ser Val Thr Thr Ser Gly Thr Gly Thr Thr Pro Thr Ile Thr Ser
100 105 110

aca act aaa aac gta gac ttt gat ctt aac aac agc tcc atc agc tcg 384
Thr Thr Lys Asn Val Asp Phe Asp Leu Asn Asn Ser Ser Ile Ser Ser
115 120 125
agc tgt gtt ttt gca acc ata gct cta cag gaa aca tcc cca gct gcc 432
Ser Cys Val Phe Ala Thr Ile Ala Leu Gln Glu Thr Ser Pro Ala Ala
130 135 140

att ccc ctt tta gat ata gcc ttc act gca cgt gtc gga gga ctt aag 480
Ile Pro Leu Leu Asp Ile Ala Phe Thr Ala Arg Val Gly Gly Leu Lys
145 150 155 160

cag tac tac cgc ctc cct ctc aat gct tac aga gac ttc act tca aat 528
Gln Tyr Tyr Arg Leu Pro Leu Asn Ala Tyr Arg Asp Phe Thr Ser Asn
165 170 175

cct tta aat gca gaa tct gaa gtt aca gat ggt ctc att gaa gtc cag 576
Pro Leu Asn Ala Glu Ser Glu Val Thr Asp Gly Leu Ile Glu Val Gln
180 185 190

tca gac tat gga att gtc tgg ggt ctg agt tta caa aaa gta ttg tgg 624
Ser Asp Tyr Gly Ile Val Trp Gly Leu Ser Leu Gln Lys Val Leu Trp
195 200 205

aaa gat gga gtg tct ttt gta ggg gtg agc gct gac tac cgt cac ggt 672
Lys Asp Gly Val Ser Phe Val Gly Val Ser Ala Asp Tyr Arg His Gly

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    210                 215                 220

tcc agt ccc atc aac tat atc atc gtt tac aac aag gcc aac ccc gag       720
Ser Ser Pro Ile Asn Tyr Ile Ile Val Tyr Asn Lys Ala Asn Pro Glu
225                 230                 235                 240

atc tat ttc gat gct act gat gga aac cta agc tat aaa gaa tgg tct       768
Ile Tyr Phe Asp Ala Thr Asp Gly Asn Leu Ser Tyr Lys Glu Trp Ser
                245                 250                 255

gca agc atc ggc atc tct acg tat ctt aat gac tat gtg ctt ccc tat       816
Ala Ser Ile Gly Ile Ser Thr Tyr Leu Asn Asp Tyr Val Leu Pro Tyr
            260                 265                 270

gca tcc gta tct ata gga aat act tca aga aaa gct cct tct gat agc       864
Ala Ser Val Ser Ile Gly Asn Thr Ser Arg Lys Ala Pro Ser Asp Ser
        275                 280                 285

ttc aca gaa ctc gaa aag caa ttt acg aat ttt aaa ttt aaa att cgt       912
Phe Thr Glu Leu Glu Lys Gln Phe Thr Asn Phe Lys Phe Lys Ile Arg
    290                 295                 300

aaa atc aca aac ttc gac aga gta aac ttc tgc ttc gga act acc tgc       960
Lys Ile Thr Asn Phe Asp Arg Val Asn Phe Cys Phe Gly Thr Thr Cys
305                 310                 315                 320

tgc atc tca aat aac ttc tac tat agt gta gaa ggc cgt tgg gga tat      1008
Cys Ile Ser Asn Asn Phe Tyr Tyr Ser Val Glu Gly Arg Trp Gly Tyr
                325                 330                 335

cag cgt gct atc aac att acg tca ggt ctg cag ttt tag                  1047
Gln Arg Ala Ile Asn Ile Thr Ser Gly Leu Gln Phe
            340                 345


<210>  8
<211>  348
<212>  PRT
<213>  Chlamydia pneumoniae

<400>  8

Gly Pro Phe Asp Met Asn Ser Lys Met Leu Lys His Leu Arg Leu Ala
1               5                   10                  15


Thr Leu Ser Phe Ser Met Phe Phe Gly Ile Val Ser Ser Pro Ala Val
            20                  25                  30


Tyr Ala Leu Gly Ala Gly Asn Pro Ala Ala Pro Val Leu Pro Gly Val
        35                  40                  45


Asn Pro Glu Gln Thr Gly Trp Cys Ala Phe Gln Leu Cys Asn Ser Tyr
    50                  55                  60
```

Asp Leu Phe Ala Ala Leu Ala Gly Ser Leu Lys Phe Gly Phe Tyr Gly
65 70 75 80

Asp Tyr Val Phe Ser Glu Ser Ala His Ile Thr Asn Val Pro Val Ile
85 90 95

Thr Ser Val Thr Thr Ser Gly Thr Gly Thr Thr Pro Thr Ile Thr Ser
100 105 110

Thr Thr Lys Asn Val Asp Phe Asp Leu Asn Asn Ser Ser Ile Ser Ser
115 120 125

Ser Cys Val Phe Ala Thr Ile Ala Leu Gln Glu Thr Ser Pro Ala Ala
130 135 140

Ile Pro Leu Leu Asp Ile Ala Phe Thr Ala Arg Val Gly Gly Leu Lys
145 150 155 160

Gln Tyr Tyr Arg Leu Pro Leu Asn Ala Tyr Arg Asp Phe Thr Ser Asn
165 170 175

Pro Leu Asn Ala Glu Ser Glu Val Thr Asp Gly Leu Ile Glu Val Gln
180 185 190

Ser Asp Tyr Gly Ile Val Trp Gly Leu Ser Leu Gln Lys Val Leu Trp
195 200 205

Lys Asp Gly Val Ser Phe Val Gly Val Ser Ala Asp Tyr Arg His Gly
210 215 220

Ser Ser Pro Ile Asn Tyr Ile Ile Val Tyr Asn Lys Ala Asn Pro Glu
225 230 235 240

Ile Tyr Phe Asp Ala Thr Asp Gly Asn Leu Ser Tyr Lys Glu Trp Ser
245 250 255

Ala Ser Ile Gly Ile Ser Thr Tyr Leu Asn Asp Tyr Val Leu Pro Tyr
260 265 270

Ala Ser Val Ser Ile Gly Asn Thr Ser Arg Lys Ala Pro Ser Asp Ser
275 280 285

Phe Thr Glu Leu Glu Lys Gln Phe Thr Asn Phe Lys Phe Lys Ile Arg
290 295 300

```
Lys Ile Thr Asn Phe Asp Arg Val Asn Phe Cys Phe Gly Thr Thr Cys
305                 310                 315                 320

Cys Ile Ser Asn Asn Phe Tyr Tyr Ser Val Glu Gly Arg Trp Gly Tyr
                325                 330                 335

Gln Arg Ala Ile Asn Ile Thr Ser Gly Leu Gln Phe
            340                 345
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<210> 9
<211> 1461
<212> DNA
<213> Chlamydia pneumoniae

<220>
<221> CDS
<222> (1)..(1461)
<223>

<400> 9

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gac agt atg atc aca cgc act aaa att att tgc act ata ggg cca gca      48
Asp Ser Met Ile Thr Arg Thr Lys Ile Ile Cys Thr Ile Gly Pro Ala
1               5                   10                  15

acg aat agt cca gag atg tta gca aaa ctt cta gat gct ggg atg aac      96
Thr Asn Ser Pro Glu Met Leu Ala Lys Leu Leu Asp Ala Gly Met Asn
            20                  25                  30

gta gca aga tta aat ttc agt cat ggg agt cac gaa act cat gga cag     144
Val Ala Arg Leu Asn Phe Ser His Gly Ser His Glu Thr His Gly Gln
        35                  40                  45

gct att gga ttt ctc aag gag tta agg gag cag aag cgg gtt cct tta     192
Ala Ile Gly Phe Leu Lys Glu Leu Arg Glu Gln Lys Arg Val Pro Leu
    50                  55                  60

gca att atg cta gat act aag ggg cct gaa att cgt tta ggg aat att     240
Ala Ile Met Leu Asp Thr Lys Gly Pro Glu Ile Arg Leu Gly Asn Ile
65                  70                  75                  80

cct cag cca att tcg gtt tct cag gga caa aag ctt cgt ctg gta agt     288
Pro Gln Pro Ile Ser Val Ser Gln Gly Gln Lys Leu Arg Leu Val Ser
                85                  90                  95

agt gat atc gat ggg agt gct gaa ggg gga gtg tct ctc tat cct aag     336
Ser Asp Ile Asp Gly Ser Ala Glu Gly Gly Val Ser Leu Tyr Pro Lys
            100                 105                 110

ggg ata ttt ccc ttt gtt cct gag ggt gct gat gtt tta ata gat gat     384
Gly Ile Phe Pro Phe Val Pro Glu Gly Ala Asp Val Leu Ile Asp Asp
        115                 120                 125
```

ggc tac att cat gct gtt gtt gtc tct tca gag gct gat tct tta gaa 432
Gly Tyr Ile His Ala Val Val Val Ser Ser Glu Ala Asp Ser Leu Glu
130 135 140

tta gag ttt atg aac agt ggc ctt ctc aag tct cat aaa tct ttg agt 480
Leu Glu Phe Met Asn Ser Gly Leu Leu Lys Ser His Lys Ser Leu Ser
145 150 155 160

atc cga ggt gtt gat gtt gct ctt ccc ttt atg aca gag aaa gat att 528
Ile Arg Gly Val Asp Val Ala Leu Pro Phe Met Thr Glu Lys Asp Ile
165 170 175

gcg gat ctt aag ttt ggg gta gag cag aat atg gat gtg gtt gct gca 576
Ala Asp Leu Lys Phe Gly Val Glu Gln Asn Met Asp Val Val Ala Ala
180 185 190

tct ttt gtg cgc tac ggt gaa gat att gaa act atg cgc aag tgt tta 624
Ser Phe Val Arg Tyr Gly Glu Asp Ile Glu Thr Met Arg Lys Cys Leu
195 200 205

gca gac tta ggc aat cct aag atg ccc atc att gca aaa ata gaa aat 672
Ala Asp Leu Gly Asn Pro Lys Met Pro Ile Ile Ala Lys Ile Glu Asn
210 215 220

cgt tta ggg gta gaa aat ttc tct aag att gcc aag ctt gcg gat gga 720
Arg Leu Gly Val Glu Asn Phe Ser Lys Ile Ala Lys Leu Ala Asp Gly
225 230 235 240

att atg att gct aga gga gat tta gga atc gag ctt tct gtc gtt gaa 768
Ile Met Ile Ala Arg Gly Asp Leu Gly Ile Glu Leu Ser Val Val Glu
245 250 255

gtc cca aat ttg caa aag atg atg gct aag gtt tct aga gaa aca ggt 816
Val Pro Asn Leu Gln Lys Met Met Ala Lys Val Ser Arg Glu Thr Gly
260 265 270

cac ttc tgt gtg act gca acg cag atg cta gaa tct atg att cgc aat 864
His Phe Cys Val Thr Ala Thr Gln Met Leu Glu Ser Met Ile Arg Asn
275 280 285

gtc tta cct aca cga gct gaa gtc tct gat att gcc aat gca att tat 912
Val Leu Pro Thr Arg Ala Glu Val Ser Asp Ile Ala Asn Ala Ile Tyr
290 295 300

gat ggt tct tca gca gtg atg ttg tca ggg gaa act gca tct gga gcc 960
Asp Gly Ser Ser Ala Val Met Leu Ser Gly Glu Thr Ala Ser Gly Ala
305 310 315 320

cat ccc gtg gct gcc gtg aaa atc atg cgt tct gtg att tta gaa aca 1008
His Pro Val Ala Ala Val Lys Ile Met Arg Ser Val Ile Leu Glu Thr
325 330 335

gaa aag aat ctc tcc cat gat tca ttc tta aaa tta gac gat agc aat 1056
Glu Lys Asn Leu Ser His Asp Ser Phe Leu Lys Leu Asp Asp Ser Asn
340 345 350

agc gct ctt cag gtg tcc ccc tat ctc tca gcc att gga ttg gca ggc 1104
Ser Ala Leu Gln Val Ser Pro Tyr Leu Ser Ala Ile Gly Leu Ala Gly

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        355                 360                 365

att cag att gca gaa agg gca gac gcc aaa gct ctt att gtt tat aca      1152
Ile Gln Ile Ala Glu Arg Ala Asp Ala Lys Ala Leu Ile Val Tyr Thr
    370                 375                 380

gaa tca gga agt tct ccg atg ttt ctc tct aaa tat cgt ccg aaa ttc      1200
Glu Ser Gly Ser Ser Pro Met Phe Leu Ser Lys Tyr Arg Pro Lys Phe
385                 390                 395                 400

cct atc att gcc gtg act cca agc act tct gtt tac tat cgc cta gct      1248
Pro Ile Ile Ala Val Thr Pro Ser Thr Ser Val Tyr Tyr Arg Leu Ala
                405                 410                 415

ttg gaa tgg ggg gtc tat cct atg ctt acc cag gaa agt gat cgc gct      1296
Leu Glu Trp Gly Val Tyr Pro Met Leu Thr Gln Glu Ser Asp Arg Ala
            420                 425                 430

gta tgg aga cat cag gcc tgt att tat ggc ata gaa cag ggc att ctc      1344
Val Trp Arg His Gln Ala Cys Ile Tyr Gly Ile Glu Gln Gly Ile Leu
        435                 440                 445

tct aat tat gat cgg att ctt gtg ctt agc aga gga gcc tgt atg gaa      1392
Ser Asn Tyr Asp Arg Ile Leu Val Leu Ser Arg Gly Ala Cys Met Glu
    450                 455                 460

gaa aca aat aat ctt acc ctg aca ata gtg aat gat att ttg act ggg      1440
Glu Thr Asn Asn Leu Thr Leu Thr Ile Val Asn Asp Ile Leu Thr Gly
465                 470                 475                 480

tcg gaa ttt cct gaa acc tag                                          1461
Ser Glu Phe Pro Glu Thr
                485


<210>  10
<211>  486
<212>  PRT
<213>  Chlamydia pneumoniae

<400>  10

Asp Ser Met Ile Thr Arg Thr Lys Ile Ile Cys Thr Ile Gly Pro Ala
1               5                   10                  15


Thr Asn Ser Pro Glu Met Leu Ala Lys Leu Leu Asp Ala Gly Met Asn
            20                  25                  30


Val Ala Arg Leu Asn Phe Ser His Gly Ser His Glu Thr His Gly Gln
        35                  40                  45


Ala Ile Gly Phe Leu Lys Glu Leu Arg Glu Gln Lys Arg Val Pro Leu
    50                  55                  60
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Ala Ile Met Leu Asp Thr Lys Gly Pro Glu Ile Arg Leu Gly Asn Ile
65 70 75 80

Pro Gln Pro Ile Ser Val Ser Gln Gly Gln Lys Leu Arg Leu Val Ser
85 90 95

Ser Asp Ile Asp Gly Ser Ala Glu Gly Gly Val Ser Leu Tyr Pro Lys
100 105 110

Gly Ile Phe Pro Phe Val Pro Glu Gly Ala Asp Val Leu Ile Asp Asp
115 120 125

Gly Tyr Ile His Ala Val Val Val Ser Ser Glu Ala Asp Ser Leu Glu
130 135 140

Leu Glu Phe Met Asn Ser Gly Leu Leu Lys Ser His Lys Ser Leu Ser
145 150 155 160

Ile Arg Gly Val Asp Val Ala Leu Pro Phe Met Thr Glu Lys Asp Ile
165 170 175

Ala Asp Leu Lys Phe Gly Val Glu Gln Asn Met Asp Val Val Ala Ala
180 185 190

Ser Phe Val Arg Tyr Gly Glu Asp Ile Glu Thr Met Arg Lys Cys Leu
195 200 205

Ala Asp Leu Gly Asn Pro Lys Met Pro Ile Ile Ala Lys Ile Glu Asn
210 215 220

Arg Leu Gly Val Glu Asn Phe Ser Lys Ile Ala Lys Leu Ala Asp Gly
225 230 235 240

Ile Met Ile Ala Arg Gly Asp Leu Gly Ile Glu Leu Ser Val Val Glu
245 250 255

Val Pro Asn Leu Gln Lys Met Met Ala Lys Val Ser Arg Glu Thr Gly
260 265 270

His Phe Cys Val Thr Ala Thr Gln Met Leu Glu Ser Met Ile Arg Asn
275 280 285

Val Leu Pro Thr Arg Ala Glu Val Ser Asp Ile Ala Asn Ala Ile Tyr
290 295 300

Asp Gly Ser Ser Ala Val Met Leu Ser Gly Glu Thr Ala Ser Gly Ala
305 310 315 320

His Pro Val Ala Ala Val Lys Ile Met Arg Ser Val Ile Leu Glu Thr
325 330 335

Glu Lys Asn Leu Ser His Asp Ser Phe Leu Lys Leu Asp Asp Ser Asn
340 345 350

Ser Ala Leu Gln Val Ser Pro Tyr Leu Ser Ala Ile Gly Leu Ala Gly
355 360 365

Ile Gln Ile Ala Glu Arg Ala Asp Ala Lys Ala Leu Ile Val Tyr Thr
370 375 380

Glu Ser Gly Ser Ser Pro Met Phe Leu Ser Lys Tyr Arg Pro Lys Phe
385 390 395 400

Pro Ile Ile Ala Val Thr Pro Ser Thr Ser Val Tyr Tyr Arg Leu Ala
405 410 415

Leu Glu Trp Gly Val Tyr Pro Met Leu Thr Gln Glu Ser Asp Arg Ala
420 425 430

Val Trp Arg His Gln Ala Cys Ile Tyr Gly Ile Glu Gln Gly Ile Leu
435 440 445

Ser Asn Tyr Asp Arg Ile Leu Val Leu Ser Arg Gly Ala Cys Met Glu
450 455 460

Glu Thr Asn Asn Leu Thr Leu Thr Ile Val Asn Asp Ile Leu Thr Gly
465 470 475 480

Ser Glu Phe Pro Glu Thr
485

<210> 11
<211> 1665
<212> DNA
<213> Chlamydia trachomatis

<220>
<221> CDS
<222> (1)..(1665)

<223>

<400> 11

tct atg cga ata gga gat cct atg aac aaa ctc atc aga cga gca gtg 48
Ser Met Arg Ile Gly Asp Pro Met Asn Lys Leu Ile Arg Arg Ala Val
1 5 10 15

acg atc ttc gcg gtg act agt gtg gcg agt tta ttt gct agc ggg gtg 96
Thr Ile Phe Ala Val Thr Ser Val Ala Ser Leu Phe Ala Ser Gly Val
20 25 30

tta gag acc tct atg gca gag tct ctc tct aca aac gtt att agc tta 144
Leu Glu Thr Ser Met Ala Glu Ser Leu Ser Thr Asn Val Ile Ser Leu
35 40 45

gct gac acc aaa gcg aaa gac aac act tct cat aaa agc aaa aaa gca 192
Ala Asp Thr Lys Ala Lys Asp Asn Thr Ser His Lys Ser Lys Lys Ala
50 55 60

aga aaa aac cac agc aaa gag act ccc gta gac cgt aaa gag gtt gct 240
Arg Lys Asn His Ser Lys Glu Thr Pro Val Asp Arg Lys Glu Val Ala
65 70 75 80

ccg gtt cat gag tct aaa gct aca gga cct aaa cag gat tct tgc ttt 288
Pro Val His Glu Ser Lys Ala Thr Gly Pro Lys Gln Asp Ser Cys Phe
85 90 95

ggc aga atg tat aca gtc aaa gtt aat gat gat cgc aat gtt gaa atc 336
Gly Arg Met Tyr Thr Val Lys Val Asn Asp Asp Arg Asn Val Glu Ile
100 105 110

aca caa gct gtt cct gaa tat gct acg gta gga tct ccc tat cct att 384
Thr Gln Ala Val Pro Glu Tyr Ala Thr Val Gly Ser Pro Tyr Pro Ile
115 120 125

gaa att act gct aca ggt aaa agg gat tgt gtt gat gtt atc att act 432
Glu Ile Thr Ala Thr Gly Lys Arg Asp Cys Val Asp Val Ile Ile Thr
130 135 140

cag caa tta cca tgt gaa gca gag ttc gta cgc agt gat cca gcg aca 480
Gln Gln Leu Pro Cys Glu Ala Glu Phe Val Arg Ser Asp Pro Ala Thr
145 150 155 160

act cct act gct gat ggt aag cta gtt tgg aaa att gac cgc tta gga 528
Thr Pro Thr Ala Asp Gly Lys Leu Val Trp Lys Ile Asp Arg Leu Gly
165 170 175

caa ggc gaa aag agt aaa att act gta tgg gta aaa cct ctt aaa gaa 576
Gln Gly Glu Lys Ser Lys Ile Thr Val Trp Val Lys Pro Leu Lys Glu
180 185 190

ggt tgc tgc ttt aca gct gca aca gta tgc gct tgt cca gag atc cgt 624
Gly Cys Cys Phe Thr Ala Ala Thr Val Cys Ala Cys Pro Glu Ile Arg
195 200 205

tcg gtt aca aaa tgt gga caa cct gct atc tgt gtt aaa caa gaa ggc 672
Ser Val Thr Lys Cys Gly Gln Pro Ala Ile Cys Val Lys Gln Glu Gly

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    210                 215                 220

cca gag aat gct tgt ttg cgt tgc cca gta gtt tac aaa att aat ata      720
Pro Glu Asn Ala Cys Leu Arg Cys Pro Val Val Tyr Lys Ile Asn Ile
225                 230                 235                 240

gtg aac caa gga aca gca aca gct cgt aac gtt gtt gtt gaa aat cct      768
Val Asn Gln Gly Thr Ala Thr Ala Arg Asn Val Val Val Glu Asn Pro
                245                 250                 255

gtt cca gat ggt tac gct cat tct tct gga cag cgt gta ctg acg ttt      816
Val Pro Asp Gly Tyr Ala His Ser Ser Gly Gln Arg Val Leu Thr Phe
            260                 265                 270

act ctt gga gat atg caa cct gga gag cac aga aca att act gta gag      864
Thr Leu Gly Asp Met Gln Pro Gly Glu His Arg Thr Ile Thr Val Glu
        275                 280                 285

ttt tgt ccg ctt aaa cgt ggt cgt gct acc aat ata gca acg gtt tct      912
Phe Cys Pro Leu Lys Arg Gly Arg Ala Thr Asn Ile Ala Thr Val Ser
    290                 295                 300

tac tgt gga gga cat aaa aat aca gca agc gta aca act gtg atc aac      960
Tyr Cys Gly Gly His Lys Asn Thr Ala Ser Val Thr Thr Val Ile Asn
305                 310                 315                 320

gag cct tgc gta caa gta agt att gca gga gca gat tgg tct tat gtt     1008
Glu Pro Cys Val Gln Val Ser Ile Ala Gly Ala Asp Trp Ser Tyr Val
                325                 330                 335

tgt aag cct gta gaa tat gtg atc tcc gtt tcc aat cct gga gat ctt     1056
Cys Lys Pro Val Glu Tyr Val Ile Ser Val Ser Asn Pro Gly Asp Leu
            340                 345                 350

gtg ttg cga gat gtc gtc gtt gaa gac act ctt tct ccc gga gtc aca     1104
Val Leu Arg Asp Val Val Val Glu Asp Thr Leu Ser Pro Gly Val Thr
        355                 360                 365

gtt ctt gaa gct gca gga gct caa att tct tgt aat aaa gta gtt tgg     1152
Val Leu Glu Ala Ala Gly Ala Gln Ile Ser Cys Asn Lys Val Val Trp
    370                 375                 380

act gtg aaa gaa ctg aat cct gga gag tct cta cag tat aaa gtt cta     1200
Thr Val Lys Glu Leu Asn Pro Gly Glu Ser Leu Gln Tyr Lys Val Leu
385                 390                 395                 400

gta aga gca caa act cct gga caa ttc aca aat aat gtt gtt gtg aag     1248
Val Arg Ala Gln Thr Pro Gly Gln Phe Thr Asn Asn Val Val Val Lys
                405                 410                 415

agc tgc tct gac tgt ggt act tgt act tct tgc gca gaa gcg aca act     1296
Ser Cys Ser Asp Cys Gly Thr Cys Thr Ser Cys Ala Glu Ala Thr Thr
            420                 425                 430

tac tgg aaa gga gtt gct gct act cat atg tgc gta gta gat act tgt     1344
Tyr Trp Lys Gly Val Ala Ala Thr His Met Cys Val Val Asp Thr Cys
        435                 440                 445
```

gac cct gtt tgt gta gga gaa aat act gtt tac cgt att tgt gtc acc 1392
Asp Pro Val Cys Val Gly Glu Asn Thr Val Tyr Arg Ile Cys Val Thr
450 455 460

aac aga ggt tct gca gaa gat aca aat gtt tct tta atg ctt aaa ttc 1440
Asn Arg Gly Ser Ala Glu Asp Thr Asn Val Ser Leu Met Leu Lys Phe
465 470 475 480

tct aaa gaa ctg caa cct gta tcc ttc tct gga cca act aaa gga acg 1488
Ser Lys Glu Leu Gln Pro Val Ser Phe Ser Gly Pro Thr Lys Gly Thr
485 490 495

att aca ggc aat aca gta gta ttc gat tcg tta cct aga tta ggt tct 1536
Ile Thr Gly Asn Thr Val Val Phe Asp Ser Leu Pro Arg Leu Gly Ser
500 505 510

aaa gaa act gta gag ttt tct gta aca ttg aaa gca gta tca gct gga 1584
Lys Glu Thr Val Glu Phe Ser Val Thr Leu Lys Ala Val Ser Ala Gly
515 520 525

gat gct cgt ggg gaa gcg att ctt tct tcc gat aca ttg act gtt cca 1632
Asp Ala Arg Gly Glu Ala Ile Leu Ser Ser Asp Thr Leu Thr Val Pro
530 535 540

gtt tct gat aca gag aat aca cac atc tat taa 1665
Val Ser Asp Thr Glu Asn Thr His Ile Tyr
545 550

<210> 12
<211> 554
<212> PRT
<213> Chlamydia trachomatis

<400> 12

Ser Met Arg Ile Gly Asp Pro Met Asn Lys Leu Ile Arg Arg Ala Val
1 5 10 15

Thr Ile Phe Ala Val Thr Ser Val Ala Ser Leu Phe Ala Ser Gly Val
20 25 30

Leu Glu Thr Ser Met Ala Glu Ser Leu Ser Thr Asn Val Ile Ser Leu
35 40 45

Ala Asp Thr Lys Ala Lys Asp Asn Thr Ser His Lys Ser Lys Lys Ala
50 55 60

Arg Lys Asn His Ser Lys Glu Thr Pro Val Asp Arg Lys Glu Val Ala
65 70 75 80

Pro Val His Glu Ser Lys Ala Thr Gly Pro Lys Gln Asp Ser Cys Phe
85 90 95

Gly Arg Met Tyr Thr Val Lys Val Asn Asp Asp Arg Asn Val Glu Ile
            100   105   110

Thr Gln Ala Val Pro Glu Tyr Ala Thr Val Gly Ser Pro Tyr Pro Ile
        115   120   125

Glu Ile Thr Ala Thr Gly Lys Arg Asp Cys Val Asp Val Ile Ile Thr
    130   135   140

Gln Gln Leu Pro Cys Glu Ala Glu Phe Val Arg Ser Asp Pro Ala Thr
145   150   155   160

Thr Pro Thr Ala Asp Gly Lys Leu Val Trp Lys Ile Asp Arg Leu Gly
                165   170   175

Gln Gly Glu Lys Ser Lys Ile Thr Val Trp Val Lys Pro Leu Lys Glu
            180   185   190

Gly Cys Cys Phe Thr Ala Ala Thr Val Cys Ala Cys Pro Glu Ile Arg
        195   200   205

Ser Val Thr Lys Cys Gly Gln Pro Ala Ile Cys Val Lys Gln Glu Gly
    210   215   220

Pro Glu Asn Ala Cys Leu Arg Cys Pro Val Val Tyr Lys Ile Asn Ile
225   230   235   240

Val Asn Gln Gly Thr Ala Thr Ala Arg Asn Val Val Val Glu Asn Pro
                245   250   255

Val Pro Asp Gly Tyr Ala His Ser Ser Gly Gln Arg Val Leu Thr Phe
            260   265   270

Thr Leu Gly Asp Met Gln Pro Gly Glu His Arg Thr Ile Thr Val Glu
        275   280   285

Phe Cys Pro Leu Lys Arg Gly Arg Ala Thr Asn Ile Ala Thr Val Ser
    290   295   300

Tyr Cys Gly Gly His Lys Asn Thr Ala Ser Val Thr Thr Val Ile Asn
305   310   315   320

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Glu Pro Cys Val Gln Val Ser Ile Ala Gly Ala Asp Trp Ser Tyr Val
                325                 330                 335

Cys Lys Pro Val Glu Tyr Val Ile Ser Val Ser Asn Pro Gly Asp Leu
            340                 345                 350

Val Leu Arg Asp Val Val Val Glu Asp Thr Leu Ser Pro Gly Val Thr
        355                 360                 365

Val Leu Glu Ala Ala Gly Ala Gln Ile Ser Cys Asn Lys Val Val Trp
    370                 375                 380

Thr Val Lys Glu Leu Asn Pro Gly Glu Ser Leu Gln Tyr Lys Val Leu
385                 390                 395                 400

Val Arg Ala Gln Thr Pro Gly Gln Phe Thr Asn Asn Val Val Val Lys
                405                 410                 415

Ser Cys Ser Asp Cys Gly Thr Cys Thr Ser Cys Ala Glu Ala Thr Thr
            420                 425                 430

Tyr Trp Lys Gly Val Ala Ala Thr His Met Cys Val Val Asp Thr Cys
        435                 440                 445

Asp Pro Val Cys Val Gly Glu Asn Thr Val Tyr Arg Ile Cys Val Thr
    450                 455                 460

Asn Arg Gly Ser Ala Glu Asp Thr Asn Val Ser Leu Met Leu Lys Phe
465                 470                 475                 480

Ser Lys Glu Leu Gln Pro Val Ser Phe Ser Gly Pro Thr Lys Gly Thr
                485                 490                 495

Ile Thr Gly Asn Thr Val Val Phe Asp Ser Leu Pro Arg Leu Gly Ser
            500                 505                 510

Lys Glu Thr Val Glu Phe Ser Val Thr Leu Lys Ala Val Ser Ala Gly
        515                 520                 525

Asp Ala Arg Gly Glu Ala Ile Leu Ser Ser Asp Thr Leu Thr Val Pro
    530                 535                 540

Val Ser Asp Thr Glu Asn Thr His Ile Tyr
545                 550
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<210> 13
<211> 1203
<212> DNA
<213> Chlamydia trachomatis

<220>
<221> CDS
<222> (1)..(1203)
<223>

<400> 13
tta tac aat tta gag gta aga atg aaa aaa ctc ttg aaa tcg gta tta 48
Leu Tyr Asn Leu Glu Val Arg Met Lys Lys Leu Leu Lys Ser Val Leu
1 5 10 15

gta ttt gcc gct ttg agt tct gct tcc tcc ttg caa gct ctg cct gtg 96
Val Phe Ala Ala Leu Ser Ser Ala Ser Ser Leu Gln Ala Leu Pro Val
20 25 30

ggg aat cct gct gaa cca agc ctt atg atc gac gga att ctg tgg gaa 144
Gly Asn Pro Ala Glu Pro Ser Leu Met Ile Asp Gly Ile Leu Trp Glu
35 40 45

ggt ttc ggc gga gat cct tgc gat cct tgc gcc act tgg tgt gac gct 192
Gly Phe Gly Gly Asp Pro Cys Asp Pro Cys Ala Thr Trp Cys Asp Ala
50 55 60

atc agc atg cgt gtt ggt tac tac gga gac ttt gtt ttc gac cgt gtt 240
Ile Ser Met Arg Val Gly Tyr Tyr Gly Asp Phe Val Phe Asp Arg Val
65 70 75 80

ttg aaa act gat gtg aat aaa gaa ttt cag atg ggt gcc aag cct aca 288
Leu Lys Thr Asp Val Asn Lys Glu Phe Gln Met Gly Ala Lys Pro Thr
85 90 95

act gat aca ggc aat agt gca gct cca tcc act ctt aca gca aga gag 336
Thr Asp Thr Gly Asn Ser Ala Ala Pro Ser Thr Leu Thr Ala Arg Glu
100 105 110

aat cct gct tac ggc cga cat atg cag gat gct gag atg ttt aca aat 384
Asn Pro Ala Tyr Gly Arg His Met Gln Asp Ala Glu Met Phe Thr Asn
115 120 125

gcc gct tgc atg gca ttg aat att tgg gat cgt ttt gat gta ttc tgt 432
Ala Ala Cys Met Ala Leu Asn Ile Trp Asp Arg Phe Asp Val Phe Cys
130 135 140

aca tta gga gcc acc agt gga tat ctt aaa gga aac tct gct tct ttc 480
Thr Leu Gly Ala Thr Ser Gly Tyr Leu Lys Gly Asn Ser Ala Ser Phe
145 150 155 160

aat tta gtt gga ttg ttt gga gat aat gaa aat caa aaa acg gtc aaa 528
Asn Leu Val Gly Leu Phe Gly Asp Asn Glu Asn Gln Lys Thr Val Lys
165 170 175

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gcg gag tct gta cca aat atg agc ttt gat caa tct gtt gtt gag ttg      576
Ala Glu Ser Val Pro Asn Met Ser Phe Asp Gln Ser Val Val Glu Leu
            180                 185                 190

tat aca gat act act ttt gcg tgg agc gtc ggc gct cgc gca gct ttg      624
Tyr Thr Asp Thr Thr Phe Ala Trp Ser Val Gly Ala Arg Ala Ala Leu
        195                 200                 205

tgg gaa tgt gga tgt gca act tta gga gct tca ttc caa tat gct caa      672
Trp Glu Cys Gly Cys Ala Thr Leu Gly Ala Ser Phe Gln Tyr Ala Gln
    210                 215                 220

tct aaa cct aaa gta gaa gaa tta aac gtt ctc tgc aat gca gca gag      720
Ser Lys Pro Lys Val Glu Glu Leu Asn Val Leu Cys Asn Ala Ala Glu
225                 230                 235                 240

ttt act att aat aaa cct aaa ggg tat gta ggt aag gag ttt cct ctt      768
Phe Thr Ile Asn Lys Pro Lys Gly Tyr Val Gly Lys Glu Phe Pro Leu
            245                 250                 255

gat ctt aca gca gga aca gat gct gcg aca gga act aag gat gcc tct      816
Asp Leu Thr Ala Gly Thr Asp Ala Ala Thr Gly Thr Lys Asp Ala Ser
            260                 265                 270

att gat tac cat gaa tgg caa gca agt tta gct ctc tct tac aga ctg      864
Ile Asp Tyr His Glu Trp Gln Ala Ser Leu Ala Leu Ser Tyr Arg Leu
        275                 280                 285

aat atg ttc act ccc tac att gga gtt aaa tgg tct cga gca agc ttt      912
Asn Met Phe Thr Pro Tyr Ile Gly Val Lys Trp Ser Arg Ala Ser Phe
    290                 295                 300

gat gcc gat acg att cgt ata gcc cag cca aaa tca gct aca gct att      960
Asp Ala Asp Thr Ile Arg Ile Ala Gln Pro Lys Ser Ala Thr Ala Ile
305                 310                 315                 320

ttt gat act acc acg ctt aac cca act att gct gga gct ggc gat gtg     1008
Phe Asp Thr Thr Thr Leu Asn Pro Thr Ile Ala Gly Ala Gly Asp Val
                325                 330                 335

aaa act ggc gca gag ggt cag ctc gga gac aca atg caa atc gtt tcc     1056
Lys Thr Gly Ala Glu Gly Gln Leu Gly Asp Thr Met Gln Ile Val Ser
            340                 345                 350

ttg caa ttg aac aag atg aaa tct aga aaa tct tgc ggt att gca gta     1104
Leu Gln Leu Asn Lys Met Lys Ser Arg Lys Ser Cys Gly Ile Ala Val
        355                 360                 365

gga aca act att gtg gat gca gac aaa tac gca gtt aca gtt gag act     1152
Gly Thr Thr Ile Val Asp Ala Asp Lys Tyr Ala Val Thr Val Glu Thr
    370                 375                 380

cgc ttg atc gat gag aga gca gct cac gta aat gca caa ttc cgc ttc     1200
Arg Leu Ile Asp Glu Arg Ala Ala His Val Asn Ala Gln Phe Arg Phe
385                 390                 395                 400

taa                                                                 1203
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<210> 14
<211> 400
<212> PRT
<213> Chlamydia trachomatis

<400> 14

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Leu Tyr Asn Leu Glu Val Arg Met Lys Lys Leu Leu Lys Ser Val Leu
1               5                   10                  15

Val Phe Ala Ala Leu Ser Ser Ala Ser Ser Leu Gln Ala Leu Pro Val
            20                  25                  30

Gly Asn Pro Ala Glu Pro Ser Leu Met Ile Asp Gly Ile Leu Trp Glu
        35                  40                  45

Gly Phe Gly Gly Asp Pro Cys Asp Pro Cys Ala Thr Trp Cys Asp Ala
    50                  55                  60

Ile Ser Met Arg Val Gly Tyr Tyr Gly Asp Phe Val Phe Asp Arg Val
65                  70                  75                  80

Leu Lys Thr Asp Val Asn Lys Glu Phe Gln Met Gly Ala Lys Pro Thr
                85                  90                  95

Thr Asp Thr Gly Asn Ser Ala Ala Pro Ser Thr Leu Thr Ala Arg Glu
            100                 105                 110

Asn Pro Ala Tyr Gly Arg His Met Gln Asp Ala Glu Met Phe Thr Asn
        115                 120                 125

Ala Ala Cys Met Ala Leu Asn Ile Trp Asp Arg Phe Asp Val Phe Cys
    130                 135                 140

Thr Leu Gly Ala Thr Ser Gly Tyr Leu Lys Gly Asn Ser Ala Ser Phe
145                 150                 155                 160

Asn Leu Val Gly Leu Phe Gly Asp Asn Glu Asn Gln Lys Thr Val Lys
                165                 170                 175

Ala Glu Ser Val Pro Asn Met Ser Phe Asp Gln Ser Val Val Glu Leu
            180                 185                 190

Tyr Thr Asp Thr Thr Phe Ala Trp Ser Val Gly Ala Arg Ala Ala Leu
        195                 200                 205
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Trp Glu Cys Gly Cys Ala Thr Leu Gly Ala Ser Phe Gln Tyr Ala Gln
    210                 215                 220

Ser Lys Pro Lys Val Glu Glu Leu Asn Val Leu Cys Asn Ala Ala Glu
225                 230                 235                     240

Phe Thr Ile Asn Lys Pro Lys Gly Tyr Val Gly Lys Glu Phe Pro Leu
                245                 250                 255

Asp Leu Thr Ala Gly Thr Asp Ala Ala Thr Gly Thr Lys Asp Ala Ser
            260                 265                 270

Ile Asp Tyr His Glu Trp Gln Ala Ser Leu Ala Leu Ser Tyr Arg Leu
        275                 280                 285

Asn Met Phe Thr Pro Tyr Ile Gly Val Lys Trp Ser Arg Ala Ser Phe
    290                 295                 300

Asp Ala Asp Thr Ile Arg Ile Ala Gln Pro Lys Ser Ala Thr Ala Ile
305                 310                 315                     320

Phe Asp Thr Thr Thr Leu Asn Pro Thr Ile Ala Gly Ala Gly Asp Val
                325                 330                 335

Lys Thr Gly Ala Glu Gly Gln Leu Gly Asp Thr Met Gln Ile Val Ser
            340                 345                 350

Leu Gln Leu Asn Lys Met Lys Ser Arg Lys Ser Cys Gly Ile Ala Val
        355                 360                 365

Gly Thr Thr Ile Val Asp Ala Asp Lys Tyr Ala Val Thr Val Glu Thr
    370                 375                 380

Arg Leu Ile Asp Glu Arg Ala Ala His Val Asn Ala Gln Phe Arg Phe
385                 390                 395                     400
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<210> 15
<211> 768
<212> DNA
<213> Chlamydia trachomatis

<220>
<221> CDS
<222> (1)..(768)

<223>

<400> 15
gca gtt ggt tgg gat gga aga ggt tct ttt atg aat cgt aga aac acg 48
Ala Val Gly Trp Asp Gly Arg Gly Ser Phe Met Asn Arg Arg Asn Thr
1 5 10 15

atg att gta gca act gct gtg aat gca gtg cta ttg gca gtg ctg ttt 96
Met Ile Val Ala Thr Ala Val Asn Ala Val Leu Leu Ala Val Leu Phe
20 25 30

atg acc gcg cgc cat tca gag caa gaa ata gag tat tct cag aaa ata 144
Met Thr Ala Arg His Ser Glu Gln Glu Ile Glu Tyr Ser Gln Lys Ile
35 40 45

gct cct att aaa atc tta gag ccc gtt ccg gtt gtt gat aag gct cca 192
Ala Pro Ile Lys Ile Leu Glu Pro Val Pro Val Val Asp Lys Ala Pro
50 55 60

gag aag tta gag aaa aag cct gag gtg att gcg aag cct tct cag gtc 240
Glu Lys Leu Glu Lys Lys Pro Glu Val Ile Ala Lys Pro Ser Gln Val
65 70 75 80

gtt aga aat cct gtc gtt tct aaa gct gaa ctt gct gcg caa ttt gca 288
Val Arg Asn Pro Val Val Ser Lys Ala Glu Leu Ala Ala Gln Phe Ala
85 90 95

gac aaa aat cct aag aca gag aag gaa tct agc ggg ggc tct aaa gag 336
Asp Lys Asn Pro Lys Thr Glu Lys Glu Ser Ser Gly Gly Ser Lys Glu
100 105 110

att tca tct acc cct gta gaa tcg acg act cct gtc gct cca gaa att 384
Ile Ser Ser Thr Pro Val Glu Ser Thr Thr Pro Val Ala Pro Glu Ile
115 120 125

tct gtt gtg aac gct aag gta gta gag aaa act cct gaa aaa gag gaa 432
Ser Val Val Asn Ala Lys Val Val Glu Lys Thr Pro Glu Lys Glu Glu
130 135 140

ttc tct act gtt att gtt aag aaa gga gac ttt tta gaa cgt ata gct 480
Phe Ser Thr Val Ile Val Lys Lys Gly Asp Phe Leu Glu Arg Ile Ala
145 150 155 160

aga tcc aat cac act aca gtt tct gca ttg atg cag ttg aat gac tta 528
Arg Ser Asn His Thr Thr Val Ser Ala Leu Met Gln Leu Asn Asp Leu
165 170 175

tct tcg aca cag tta cag ata gga caa gtg tta cga gtt cct aaa acg 576
Ser Ser Thr Gln Leu Gln Ile Gly Gln Val Leu Arg Val Pro Lys Thr
180 185 190

aat aag aca gag aag gat ctt caa gtg aag act cca aat ctg gaa gat 624
Asn Lys Thr Glu Lys Asp Leu Gln Val Lys Thr Pro Asn Leu Glu Asp
195 200 205

tac tat gta gtc aag gaa gga gat agt cct tgg gcc att gca ttg agt 672
Tyr Tyr Val Val Lys Glu Gly Asp Ser Pro Trp Ala Ile Ala Leu Ser

210 215 220

aat ggt att cgt ttg gat gag ctg ttg aag tta aat gga tta gat gag 720
Asn Gly Ile Arg Leu Asp Glu Leu Leu Lys Leu Asn Gly Leu Asp Glu
225 230 235 240

cag aaa gct cgt aga tta cgt cca ggg gat aga tta cga att cga taa 768
Gln Lys Ala Arg Arg Leu Arg Pro Gly Asp Arg Leu Arg Ile Arg
245 250 255

<210> 16
<211> 255
<212> PRT
<213> Chlamydia trachomatis

<400> 16

Ala Val Gly Trp Asp Gly Arg Gly Ser Phe Met Asn Arg Arg Asn Thr
1 5 10 15

Met Ile Val Ala Thr Ala Val Asn Ala Val Leu Leu Ala Val Leu Phe
20 25 30

Met Thr Ala Arg His Ser Glu Gln Glu Ile Glu Tyr Ser Gln Lys Ile
35 40 45

Ala Pro Ile Lys Ile Leu Glu Pro Val Pro Val Val Asp Lys Ala Pro
50 55 60

Glu Lys Leu Glu Lys Lys Pro Glu Val Ile Ala Lys Pro Ser Gln Val
65 70 75 80

Val Arg Asn Pro Val Val Ser Lys Ala Glu Leu Ala Ala Gln Phe Ala
85 90 95

Asp Lys Asn Pro Lys Thr Glu Lys Glu Ser Ser Gly Gly Ser Lys Glu
100 105 110

Ile Ser Ser Thr Pro Val Glu Ser Thr Thr Pro Val Ala Pro Glu Ile
115 120 125

Ser Val Val Asn Ala Lys Val Val Glu Lys Thr Pro Glu Lys Glu Glu
130 135 140

Phe Ser Thr Val Ile Val Lys Lys Gly Asp Phe Leu Glu Arg Ile Ala
145 150 155 160

Arg Ser Asn His Thr Thr Val Ser Ala Leu Met Gln Leu Asn Asp Leu
165 170 175

Ser Ser Thr Gln Leu Gln Ile Gly Gln Val Leu Arg Val Pro Lys Thr
180 185 190

Asn Lys Thr Glu Lys Asp Leu Gln Val Lys Thr Pro Asn Leu Glu Asp
195 200 205

Tyr Tyr Val Val Lys Glu Gly Asp Ser Pro Trp Ala Ile Ala Leu Ser
210 215 220

Asn Gly Ile Arg Leu Asp Glu Leu Leu Lys Leu Asn Gly Leu Asp Glu
225 230 235 240

Gln Lys Ala Arg Arg Leu Arg Pro Gly Asp Arg Leu Arg Ile Arg
245 250 255

<210> 17
<211> 1494
<212> DNA
<213> Chlamydia trachomatis

<220>
<221> CDS
<222> (1)..(1494)
<223>

<400> 17
aag ata ttc tac tca cta ata ccg gta tcc cga ttt atg atc gct aga 48
Lys Ile Phe Tyr Ser Leu Ile Pro Val Ser Arg Phe Met Ile Ala Arg
1 5 10 15

acg aaa att att tgt acg ata ggc cct gca acg aat acc cct gag atg 96
Thr Lys Ile Ile Cys Thr Ile Gly Pro Ala Thr Asn Thr Pro Glu Met
20 25 30

ctg gaa aag ctt ctt gat gca ggg atg aat gta gct cgc ctt aat ttt 144
Leu Glu Lys Leu Leu Asp Ala Gly Met Asn Val Ala Arg Leu Asn Phe
35 40 45

agc cac ggg acc cat gaa agc cat ggc cgg acc atc gct att ctt aaa 192
Ser His Gly Thr His Glu Ser His Gly Arg Thr Ile Ala Ile Leu Lys
50 55 60

gaa cta cga gag aag cgc caa gtt cct tta gct att atg cta gat aca 240
Glu Leu Arg Glu Lys Arg Gln Val Pro Leu Ala Ile Met Leu Asp Thr
65 70 75 80

aaa ggt ccc gaa att cgt tta ggc caa gta gaa tct cct ata aaa gta 288
Lys Gly Pro Glu Ile Arg Leu Gly Gln Val Glu Ser Pro Ile Lys Val

85 90 95

cag cct ggg gat cgt ctt act ctc gtt agc aaa gaa att tta gga tcc 336
Gln Pro Gly Asp Arg Leu Thr Leu Val Ser Lys Glu Ile Leu Gly Ser
100 105 110

aaa gaa agc ggc gtt act ctt tat cca agt tgt gta ttc cct tat gtt 384
Lys Glu Ser Gly Val Thr Leu Tyr Pro Ser Cys Val Phe Pro Tyr Val
115 120 125

aga gaa cga gct cct gtt ctc att gat gat ggg tat atc caa gca gtg 432
Arg Glu Arg Ala Pro Val Leu Ile Asp Asp Gly Tyr Ile Gln Ala Val
130 135 140

gtg gtc aat gct caa gag cat atg gtg gaa ata gag ttt caa aat tca 480
Val Val Asn Ala Gln Glu His Met Val Glu Ile Glu Phe Gln Asn Ser
145 150 155 160

gga gaa ata aaa tcc aac aaa tct ctt agc atc aaa gat atc gat gtt 528
Gly Glu Ile Lys Ser Asn Lys Ser Leu Ser Ile Lys Asp Ile Asp Val
165 170 175

gct ctt cct ttc atg aca gag aag gat att gca gac tta aaa ttt ggg 576
Ala Leu Pro Phe Met Thr Glu Lys Asp Ile Ala Asp Leu Lys Phe Gly
180 185 190

gta gaa caa gaa ctc gat ctt atc gct gct tcg ttc gtc aga tgt aat 624
Val Glu Gln Glu Leu Asp Leu Ile Ala Ala Ser Phe Val Arg Cys Asn
195 200 205

gaa gat att gac agc atg cgt aaa gtt ttg gaa agc ttt ggt cgt cct 672
Glu Asp Ile Asp Ser Met Arg Lys Val Leu Glu Ser Phe Gly Arg Pro
210 215 220

aat atg ccc atc att gct aaa ata gaa aat cat tta gga gta caa aat 720
Asn Met Pro Ile Ile Ala Lys Ile Glu Asn His Leu Gly Val Gln Asn
225 230 235 240

ttc caa gag atc gct aga gct gct gat ggt atc atg att gca cgc ggg 768
Phe Gln Glu Ile Ala Arg Ala Ala Asp Gly Ile Met Ile Ala Arg Gly
245 250 255

gat ctt ggt att gaa ttg tct att gtt gaa gtt cct gga cta caa aaa 816
Asp Leu Gly Ile Glu Leu Ser Ile Val Glu Val Pro Gly Leu Gln Lys
260 265 270

ttt atg gcc cga gca tcg agg gaa acg ggt cgg ttt tgt atc act gca 864
Phe Met Ala Arg Ala Ser Arg Glu Thr Gly Arg Phe Cys Ile Thr Ala
275 280 285

acg caa atg ctc gag tca atg att cgc aac ccc ctt cct aca cga gcc 912
Thr Gln Met Leu Glu Ser Met Ile Arg Asn Pro Leu Pro Thr Arg Ala
290 295 300

gaa gtc tct gac gtt gcc aac gcc att tac gat gga acc tct gca gtc 960
Glu Val Ser Asp Val Ala Asn Ala Ile Tyr Asp Gly Thr Ser Ala Val
305 310 315 320

atg ttg tct gga gaa act gcc tta gga gcc cat cct gta cat gca gta 1008
Met Leu Ser Gly Glu Thr Ala Leu Gly Ala His Pro Val His Ala Val
325 330 335

aaa aca atg cgt tcc att atc caa gag act gag aag act ttc gat tac 1056
Lys Thr Met Arg Ser Ile Ile Gln Glu Thr Glu Lys Thr Phe Asp Tyr
340 345 350

cac gct ttt ttc cag ctg aac gac aaa aac agc gct ctc aaa gtt tct 1104
His Ala Phe Phe Gln Leu Asn Asp Lys Asn Ser Ala Leu Lys Val Ser
355 360 365

cct tat ctt gaa gcc att ggg ttt tct gga atc caa att gca gaa aaa 1152
Pro Tyr Leu Glu Ala Ile Gly Phe Ser Gly Ile Gln Ile Ala Glu Lys
370 375 380

gca tct gcc aaa gcc att att gtg tat acc cag acg gga gga tct ccg 1200
Ala Ser Ala Lys Ala Ile Ile Val Tyr Thr Gln Thr Gly Gly Ser Pro
385 390 395 400

atg ttt tta tcc aaa tat cga cct tat ctc cct att att gct gtt acc 1248
Met Phe Leu Ser Lys Tyr Arg Pro Tyr Leu Pro Ile Ile Ala Val Thr
405 410 415

cct aac cgc aat gtg tac tat cgt tta gct gta gaa tgg gga gta tat 1296
Pro Asn Arg Asn Val Tyr Tyr Arg Leu Ala Val Glu Trp Gly Val Tyr
420 425 430

cct atg cta acc cta gaa tcg aac cgt aca gtc tgg cgt cac caa gct 1344
Pro Met Leu Thr Leu Glu Ser Asn Arg Thr Val Trp Arg His Gln Ala
435 440 445

tgt gta tat gga gta gaa aaa gga att ctt tct aac tat gat aaa att 1392
Cys Val Tyr Gly Val Glu Lys Gly Ile Leu Ser Asn Tyr Asp Lys Ile
450 455 460

ctt gtc ttc agc cgc gga gct ggg atg caa gac acc aac aat ctc acc 1440
Leu Val Phe Ser Arg Gly Ala Gly Met Gln Asp Thr Asn Asn Leu Thr
465 470 475 480

ttg aca act gtg cat gat gtg cta tcc ccc tct ctt gac gag ata gtt 1488
Leu Thr Thr Val His Asp Val Leu Ser Pro Ser Leu Asp Glu Ile Val
485 490 495

cca taa 1494
Pro

<210> 18
<211> 497
<212> PRT
<213> Chlamydia trachomatis

<400> 18

Lys Ile Phe Tyr Ser Leu Ile Pro Val Ser Arg Phe Met Ile Ala Arg
1 5 10 15

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Thr Lys Ile Ile Cys Thr Ile Gly Pro Ala Thr Asn Thr Pro Glu Met
            20                  25                  30

Leu Glu Lys Leu Leu Asp Ala Gly Met Asn Val Ala Arg Leu Asn Phe
        35                  40                  45

Ser His Gly Thr His Glu Ser His Gly Arg Thr Ile Ala Ile Leu Lys
    50                  55                  60

Glu Leu Arg Glu Lys Arg Gln Val Pro Leu Ala Ile Met Leu Asp Thr
65                  70                  75                  80

Lys Gly Pro Glu Ile Arg Leu Gly Gln Val Glu Ser Pro Ile Lys Val
                85                  90                  95

Gln Pro Gly Asp Arg Leu Thr Leu Val Ser Lys Glu Ile Leu Gly Ser
            100                 105                 110

Lys Glu Ser Gly Val Thr Leu Tyr Pro Ser Cys Val Phe Pro Tyr Val
        115                 120                 125

Arg Glu Arg Ala Pro Val Leu Ile Asp Asp Gly Tyr Ile Gln Ala Val
    130                 135                 140

Val Val Asn Ala Gln Glu His Met Val Glu Ile Glu Phe Gln Asn Ser
145                 150                 155                 160

Gly Glu Ile Lys Ser Asn Lys Ser Leu Ser Ile Lys Asp Ile Asp Val
                165                 170                 175

Ala Leu Pro Phe Met Thr Glu Lys Asp Ile Ala Asp Leu Lys Phe Gly
            180                 185                 190

Val Glu Gln Glu Leu Asp Leu Ile Ala Ala Ser Phe Val Arg Cys Asn
        195                 200                 205

Glu Asp Ile Asp Ser Met Arg Lys Val Leu Glu Ser Phe Gly Arg Pro
    210                 215                 220

Asn Met Pro Ile Ile Ala Lys Ile Glu Asn His Leu Gly Val Gln Asn
225                 230                 235                 240
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Phe Gln Glu Ile Ala Arg Ala Ala Asp Gly Ile Met Ile Ala Arg Gly
245 250 255

Asp Leu Gly Ile Glu Leu Ser Ile Val Glu Val Pro Gly Leu Gln Lys
260 265 270

Phe Met Ala Arg Ala Ser Arg Glu Thr Gly Arg Phe Cys Ile Thr Ala
275 280 285

Thr Gln Met Leu Glu Ser Met Ile Arg Asn Pro Leu Pro Thr Arg Ala
290 295 300

Glu Val Ser Asp Val Ala Asn Ala Ile Tyr Asp Gly Thr Ser Ala Val
305 310 315 320

Met Leu Ser Gly Glu Thr Ala Leu Gly Ala His Pro Val His Ala Val
325 330 335

Lys Thr Met Arg Ser Ile Ile Gln Glu Thr Glu Lys Thr Phe Asp Tyr
340 345 350

His Ala Phe Phe Gln Leu Asn Asp Lys Asn Ser Ala Leu Lys Val Ser
355 360 365

Pro Tyr Leu Glu Ala Ile Gly Phe Ser Gly Ile Gln Ile Ala Glu Lys
370 375 380

Ala Ser Ala Lys Ala Ile Ile Val Tyr Thr Gln Thr Gly Gly Ser Pro
385 390 395 400

Met Phe Leu Ser Lys Tyr Arg Pro Tyr Leu Pro Ile Ile Ala Val Thr
405 410 415

Pro Asn Arg Asn Val Tyr Tyr Arg Leu Ala Val Glu Trp Gly Val Tyr
420 425 430

Pro Met Leu Thr Leu Glu Ser Asn Arg Thr Val Trp Arg His Gln Ala
435 440 445

Cys Val Tyr Gly Val Glu Lys Gly Ile Leu Ser Asn Tyr Asp Lys Ile
450 455 460

Leu Val Phe Ser Arg Gly Ala Gly Met Gln Asp Thr Asn Asn Leu Thr
465 470 475 480

Leu Thr Thr Val His Asp Val Leu Ser Pro Ser Leu Asp Glu Ile Val
485 490 495

Pro

<210> 19
<211> 1161
<212> DNA
<213> Chlamydia trachomatis

<220>
<221> CDS
<222> (1)..(1161)
<223>

<400> 19
atg aaa aaa ctc ttg aaa tcg gta tta gca ttt gcc gtt ttg ggt tct 48
Met Lys Lys Leu Leu Lys Ser Val Leu Ala Phe Ala Val Leu Gly Ser
1 5 10 15

gct tcc tcc ttg cat gct ctg cct gtg ggg aat cct gct gaa cca agc 96
Ala Ser Ser Leu His Ala Leu Pro Val Gly Asn Pro Ala Glu Pro Ser
20 25 30

ctt atg att gac ggg att ctt tgg gaa ggt ttc ggt gga gat cct tgc 144
Leu Met Ile Asp Gly Ile Leu Trp Glu Gly Phe Gly Gly Asp Pro Cys
35 40 45

gat cct tgc aca act tgg tgt gat gcc atc agc cta cgt ctc ggc tac 192
Asp Pro Cys Thr Thr Trp Cys Asp Ala Ile Ser Leu Arg Leu Gly Tyr
50 55 60

tat ggg gac ttc gtt ttt gat cgt gtt ttg aaa aca gac gtg aac aaa 240
Tyr Gly Asp Phe Val Phe Asp Arg Val Leu Lys Thr Asp Val Asn Lys
65 70 75 80

cag ttc gaa atg gga gca gct cct aca gga gat gca gac ctt act aca 288
Gln Phe Glu Met Gly Ala Ala Pro Thr Gly Asp Ala Asp Leu Thr Thr
85 90 95

gca cct act cct gca tca aga gag aat ccc gct tat ggc aag cat atg 336
Ala Pro Thr Pro Ala Ser Arg Glu Asn Pro Ala Tyr Gly Lys His Met
100 105 110

caa gat gca gaa atg ttc act aat gct gcg tac atg gct tta aac att 384
Gln Asp Ala Glu Met Phe Thr Asn Ala Ala Tyr Met Ala Leu Asn Ile
115 120 125

tgg gac cgt ttc gat gta ttt tgt aca ttg gga gca act agc gga tat 432
Trp Asp Arg Phe Asp Val Phe Cys Thr Leu Gly Ala Thr Ser Gly Tyr
130 135 140

ctt aaa ggt aat tct gcc gcc ttt aac tta gtt ggt ctg ttt gga aga 480
Leu Lys Gly Asn Ser Ala Ala Phe Asn Leu Val Gly Leu Phe Gly Arg
145 150 155 160

gat gaa act gca gtt gca gct gac gac ata cct aac gtc agc ttg tct 528
Asp Glu Thr Ala Val Ala Ala Asp Asp Ile Pro Asn Val Ser Leu Ser
165 170 175

caa gct gtt gtc gaa ctc tac aca gac aca gct ttc gct tgg agc gtc 576
Gln Ala Val Val Glu Leu Tyr Thr Asp Thr Ala Phe Ala Trp Ser Val
180 185 190

ggt gct aga gca gct tta tgg gag tgc gga tgt gca act tta gga gct 624
Gly Ala Arg Ala Ala Leu Trp Glu Cys Gly Cys Ala Thr Leu Gly Ala
195 200 205

tcc ttc caa tat gct caa tct aag cca aaa gta gag gaa tta aac gtt 672
Ser Phe Gln Tyr Ala Gln Ser Lys Pro Lys Val Glu Glu Leu Asn Val
210 215 220

ctc tgt aat gcg gca gaa ttc act att aac aag cct aaa gga tac gtt 720
Leu Cys Asn Ala Ala Glu Phe Thr Ile Asn Lys Pro Lys Gly Tyr Val
225 230 235 240

gga caa gag ttt cct ctt aac att aaa gct gga aca gtt agc gct aca 768
Gly Gln Glu Phe Pro Leu Asn Ile Lys Ala Gly Thr Val Ser Ala Thr
245 250 255

gat act aaa gat gct tcc atc gat tac cat gag tgg caa gca agc ttg 816
Asp Thr Lys Asp Ala Ser Ile Asp Tyr His Glu Trp Gln Ala Ser Leu
260 265 270

gct ttg tct tac aga ctg aat atg ttc act cct tac att gga gtt aag 864
Ala Leu Ser Tyr Arg Leu Asn Met Phe Thr Pro Tyr Ile Gly Val Lys
275 280 285

tgg tct aga gca agc ttt gat gcc gac act atc cgc att gcg cag cct 912
Trp Ser Arg Ala Ser Phe Asp Ala Asp Thr Ile Arg Ile Ala Gln Pro
290 295 300

kag ctt gag acc tct atc tta aka atg acc act tgg aac cca acg atc 960
Xaa Leu Glu Thr Ser Ile Leu Xaa Met Thr Thr Trp Asn Pro Thr Ile
305 310 315 320

tct gga tct ggt ata gac gtt gat aca aaa atc acg gat aca tta caa 1008
Ser Gly Ser Gly Ile Asp Val Asp Thr Lys Ile Thr Asp Thr Leu Gln
325 330 335

att gtt tcc ttg cag ctc aac aag atg aaa tcc aga aaa tct tgc ggt 1056
Ile Val Ser Leu Gln Leu Asn Lys Met Lys Ser Arg Lys Ser Cys Gly
340 345 350

ctt gca att gga aca aca att gta gat gct gat aaa tat gca gtt act 1104
Leu Ala Ile Gly Thr Thr Ile Val Asp Ala Asp Lys Tyr Ala Val Thr
355 360 365

gtt gag aca cgc ttg atc gat gaa aga gca gct cac gta aat gct cag 1152
Val Glu Thr Arg Leu Ile Asp Glu Arg Ala Ala His Val Asn Ala Gln

370 375 380

ttc cgt ttc 1161
Phe Arg Phe
385

<210> 20
<211> 387
<212> PRT
<213> Chlamydia trachomatis

<220>
<221> misc_feature
<222> (305)..(305)
<223> The 'Xaa' at location 305 stands for Glu, or a stop codon.

<220>
<221> misc_feature
<222> (312)..(312)
<223> The 'Xaa' at location 312 stands for Arg, or Ile.

<400> 20

Met Lys Lys Leu Leu Lys Ser Val Leu Ala Phe Ala Val Leu Gly Ser
1 5 10 15

Ala Ser Ser Leu His Ala Leu Pro Val Gly Asn Pro Ala Glu Pro Ser
20 25 30

Leu Met Ile Asp Gly Ile Leu Trp Glu Gly Phe Gly Gly Asp Pro Cys
35 40 45

Asp Pro Cys Thr Thr Trp Cys Asp Ala Ile Ser Leu Arg Leu Gly Tyr
50 55 60

Tyr Gly Asp Phe Val Phe Asp Arg Val Leu Lys Thr Asp Val Asn Lys
65 70 75 80

Gln Phe Glu Met Gly Ala Ala Pro Thr Gly Asp Ala Asp Leu Thr Thr
85 90 95

Ala Pro Thr Pro Ala Ser Arg Glu Asn Pro Ala Tyr Gly Lys His Met
100 105 110

Gln Asp Ala Glu Met Phe Thr Asn Ala Ala Tyr Met Ala Leu Asn Ile
115 120 125

Trp Asp Arg Phe Asp Val Phe Cys Thr Leu Gly Ala Thr Ser Gly Tyr
130 135 140

Leu Lys Gly Asn Ser Ala Ala Phe Asn Leu Val Gly Leu Phe Gly Arg
145 150 155 160

Asp Glu Thr Ala Val Ala Ala Asp Asp Ile Pro Asn Val Ser Leu Ser
165 170 175

Gln Ala Val Val Glu Leu Tyr Thr Asp Thr Ala Phe Ala Trp Ser Val
180 185 190

Gly Ala Arg Ala Ala Leu Trp Glu Cys Gly Cys Ala Thr Leu Gly Ala
195 200 205

Ser Phe Gln Tyr Ala Gln Ser Lys Pro Lys Val Glu Glu Leu Asn Val
210 215 220

Leu Cys Asn Ala Ala Glu Phe Thr Ile Asn Lys Pro Lys Gly Tyr Val
225 230 235 240

Gly Gln Glu Phe Pro Leu Asn Ile Lys Ala Gly Thr Val Ser Ala Thr
245 250 255

Asp Thr Lys Asp Ala Ser Ile Asp Tyr His Glu Trp Gln Ala Ser Leu
260 265 270

Ala Leu Ser Tyr Arg Leu Asn Met Phe Thr Pro Tyr Ile Gly Val Lys
275 280 285

Trp Ser Arg Ala Ser Phe Asp Ala Asp Thr Ile Arg Ile Ala Gln Pro
290 295 300

Xaa Leu Glu Thr Ser Ile Leu Xaa Met Thr Thr Trp Asn Pro Thr Ile
305 310 315 320

Ser Gly Ser Gly Ile Asp Val Asp Thr Lys Ile Thr Asp Thr Leu Gln
325 330 335

Ile Val Ser Leu Gln Leu Asn Lys Met Lys Ser Arg Lys Ser Cys Gly
340 345 350

Leu Ala Ile Gly Thr Thr Ile Val Asp Ala Asp Lys Tyr Ala Val Thr
355 360 365

Val Glu Thr Arg Leu Ile Asp Glu Arg Ala Ala His Val Asn Ala Gln
370 375 380

Phe Arg Phe
385

<210> 21
<211> 1443
<212> DNA
<213> Chlamydia trachomatis

<220>
<221> CDS
<222> (1)..(1443)
<223>

<400> 21
atg atc gct aga aca aaa att att tgt aca ata ggc cct gca aca aac 48
Met Ile Ala Arg Thr Lys Ile Ile Cys Thr Ile Gly Pro Ala Thr Asn
1 5 10 15

acc cca gaa atg ctt gaa aaa ctt ctt gat gcg ggg atg aat gta gcg 96
Thr Pro Glu Met Leu Glu Lys Leu Leu Asp Ala Gly Met Asn Val Ala
20 25 30

cgt ctt aac ttc agt cat ggt acc cac gaa agc cac ggc cgg acc att 144
Arg Leu Asn Phe Ser His Gly Thr His Glu Ser His Gly Arg Thr Ile
35 40 45

gct att ctt aag gaa cta cgc gaa aag cgc caa gtc cct tta gct att 192
Ala Ile Leu Lys Glu Leu Arg Glu Lys Arg Gln Val Pro Leu Ala Ile
50 55 60

atg ttg gat aca aaa gga cca gaa att cgt tta ggc caa gta gaa tct 240
Met Leu Asp Thr Lys Gly Pro Glu Ile Arg Leu Gly Gln Val Glu Ser
65 70 75 80

cct ata aaa gtg aag cca gga gac cgt ctc act tta acc agt aaa gaa 288
Pro Ile Lys Val Lys Pro Gly Asp Arg Leu Thr Leu Thr Ser Lys Glu
85 90 95

att ttg gga tcc aaa gaa gct gga gtc act ctt tat cct agc tgc gtg 336
Ile Leu Gly Ser Lys Glu Ala Gly Val Thr Leu Tyr Pro Ser Cys Val
100 105 110

ttc cct ttc gtt cgc gaa cgc gct ccc gtc ctg att gat gat gga tat 384
Phe Pro Phe Val Arg Glu Arg Ala Pro Val Leu Ile Asp Asp Gly Tyr
115 120 125

atc caa gcc gta gtt gtc aat gct caa gag cat ctc att gag ata gaa 432
Ile Gln Ala Val Val Val Asn Ala Gln Glu His Leu Ile Glu Ile Glu
130 135 140

ttt cag aat tca gga gaa atc aag tct aat aaa tca ctt agc atc aaa 480
Phe Gln Asn Ser Gly Glu Ile Lys Ser Asn Lys Ser Leu Ser Ile Lys

145 150 155 160

gat ata gac gta gcc ctc ccc ttc atg aca gag aag gat atc acg gat 528
Asp Ile Asp Val Ala Leu Pro Phe Met Thr Glu Lys Asp Ile Thr Asp
165 170 175

cta aaa ttc ggg gtc gaa caa gaa ctt gac ctt atc gca gca tct ttt 576
Leu Lys Phe Gly Val Glu Gln Glu Leu Asp Leu Ile Ala Ala Ser Phe
180 185 190

gtc cga tgt aac gaa gac atc gat agc atg cgt aaa gtt tta gaa aac 624
Val Arg Cys Asn Glu Asp Ile Asp Ser Met Arg Lys Val Leu Glu Asn
195 200 205

ttc ggc cgg cca aat atg ccg atc att gcc aaa ata gaa aat cat tta 672
Phe Gly Arg Pro Asn Met Pro Ile Ile Ala Lys Ile Glu Asn His Leu
210 215 220

ggg gta caa aat ttc caa gaa ata gcc aaa gct tct gat gga att atg 720
Gly Val Gln Asn Phe Gln Glu Ile Ala Lys Ala Ser Asp Gly Ile Met
225 230 235 240

atc gca cga gga gat ctc ggc atc gaa tta tct atc gtt gaa gtc cct 768
Ile Ala Arg Gly Asp Leu Gly Ile Glu Leu Ser Ile Val Glu Val Pro
245 250 255

gcc tta caa aaa ttt atg gct cgt gtg tcc aga gaa aca ggc cgt ttt 816
Ala Leu Gln Lys Phe Met Ala Arg Val Ser Arg Glu Thr Gly Arg Phe
260 265 270

tgt atc acc gca aca caa atg ctc gag tca atg att cgc aat ccc ctt 864
Cys Ile Thr Ala Thr Gln Met Leu Glu Ser Met Ile Arg Asn Pro Leu
275 280 285

cct aca cga gcc gaa gtt tcc gat gta gct aat gct atc cac gat gga 912
Pro Thr Arg Ala Glu Val Ser Asp Val Ala Asn Ala Ile His Asp Gly
290 295 300

act tcc gct gtg atg tta tca gga gaa act gct tca gga act tat cct 960
Thr Ser Ala Val Met Leu Ser Gly Glu Thr Ala Ser Gly Thr Tyr Pro
305 310 315 320

ata gaa gct gta aaa act atg cgc tcg atc atc caa gaa acg gaa aaa 1008
Ile Glu Ala Val Lys Thr Met Arg Ser Ile Ile Gln Glu Thr Glu Lys
325 330 335

tcc ttt gat tac caa gcc ttt ttc caa ctc aat gac aaa aat agc gct 1056
Ser Phe Asp Tyr Gln Ala Phe Phe Gln Leu Asn Asp Lys Asn Ser Ala
340 345 350

ctc aaa gtc tct cct tat ctt gaa gca ata ggc gct tca ggg atc caa 1104
Leu Lys Val Ser Pro Tyr Leu Glu Ala Ile Gly Ala Ser Gly Ile Gln
355 360 365

atc gct gag aaa gct tct gct aaa gcg att att gta tac acc caa act 1152
Ile Ala Glu Lys Ala Ser Ala Lys Ala Ile Ile Val Tyr Thr Gln Thr
370 375 380

```
ggg gga tct ccc atg ttt ctt tct aaa tat cgt ccc tat ctc ccc att      1200
Gly Gly Ser Pro Met Phe Leu Ser Lys Tyr Arg Pro Tyr Leu Pro Ile
385                 390                 395                 400

att gcc gtt acc cca aac cgc aat gta tac tat cgc tta gca gta gaa      1248
Ile Ala Val Thr Pro Asn Arg Asn Val Tyr Tyr Arg Leu Ala Val Glu
                405                 410                 415

tgg ggc gta tac cct atg cta acc tca gaa tct aac cga aca gtt tgg      1296
Trp Gly Val Tyr Pro Met Leu Thr Ser Glu Ser Asn Arg Thr Val Trp
            420                 425                 430

cgc cac caa gct tgt gtc tat gga gta gag aaa gga atc ctt tca aac      1344
Arg His Gln Ala Cys Val Tyr Gly Val Glu Lys Gly Ile Leu Ser Asn
        435                 440                 445

tat gat aaa att ctt gtt ttt agc cga gga gca ggg atg cag gac acg      1392
Tyr Asp Lys Ile Leu Val Phe Ser Arg Gly Ala Gly Met Gln Asp Thr
    450                 455                 460

aat aac ctt act ctg act act gta aac gat gtt tta tct cct tct ctt      1440
Asn Asn Leu Thr Leu Thr Thr Val Asn Asp Val Leu Ser Pro Ser Leu
465                 470                 475                 480

gaa                                                                  1443
Glu


<210>  22
<211>  481
<212>  PRT
<213>  Chlamydia trachomatis

<400>  22

Met Ile Ala Arg Thr Lys Ile Ile Cys Thr Ile Gly Pro Ala Thr Asn
1               5                   10                  15

Thr Pro Glu Met Leu Glu Lys Leu Leu Asp Ala Gly Met Asn Val Ala
            20                  25                  30

Arg Leu Asn Phe Ser His Gly Thr His Glu Ser His Gly Arg Thr Ile
        35                  40                  45

Ala Ile Leu Lys Glu Leu Arg Glu Lys Arg Gln Val Pro Leu Ala Ile
    50                  55                  60

Met Leu Asp Thr Lys Gly Pro Glu Ile Arg Leu Gly Gln Val Glu Ser
65                  70                  75                  80

Pro Ile Lys Val Lys Pro Gly Asp Arg Leu Thr Leu Thr Ser Lys Glu
                85                  90                  95
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Ile Leu Gly Ser Lys Glu Ala Gly Val Thr Leu Tyr Pro Ser Cys Val
            100                 105                 110

Phe Pro Phe Val Arg Glu Arg Ala Pro Val Leu Ile Asp Asp Gly Tyr
        115                 120                 125

Ile Gln Ala Val Val Val Asn Ala Gln Glu His Leu Ile Glu Ile Glu
    130                 135                 140

Phe Gln Asn Ser Gly Glu Ile Lys Ser Asn Lys Ser Leu Ser Ile Lys
145                 150                 155                 160

Asp Ile Asp Val Ala Leu Pro Phe Met Thr Glu Lys Asp Ile Thr Asp
                165                 170                 175

Leu Lys Phe Gly Val Glu Gln Glu Leu Asp Leu Ile Ala Ala Ser Phe
            180                 185                 190

Val Arg Cys Asn Glu Asp Ile Asp Ser Met Arg Lys Val Leu Glu Asn
        195                 200                 205

Phe Gly Arg Pro Asn Met Pro Ile Ile Ala Lys Ile Glu Asn His Leu
    210                 215                 220

Gly Val Gln Asn Phe Gln Glu Ile Ala Lys Ala Ser Asp Gly Ile Met
225                 230                 235                 240

Ile Ala Arg Gly Asp Leu Gly Ile Glu Leu Ser Ile Val Glu Val Pro
                245                 250                 255

Ala Leu Gln Lys Phe Met Ala Arg Val Ser Arg Glu Thr Gly Arg Phe
            260                 265                 270

Cys Ile Thr Ala Thr Gln Met Leu Glu Ser Met Ile Arg Asn Pro Leu
        275                 280                 285

Pro Thr Arg Ala Glu Val Ser Asp Val Ala Asn Ala Ile His Asp Gly
    290                 295                 300

Thr Ser Ala Val Met Leu Ser Gly Glu Thr Ala Ser Gly Thr Tyr Pro
305                 310                 315                 320
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Ile Glu Ala Val Lys Thr Met Arg Ser Ile Ile Gln Glu Thr Glu Lys
325 330 335

Ser Phe Asp Tyr Gln Ala Phe Phe Gln Leu Asn Asp Lys Asn Ser Ala
340 345 350

Leu Lys Val Ser Pro Tyr Leu Glu Ala Ile Gly Ala Ser Gly Ile Gln
355 360 365

Ile Ala Glu Lys Ala Ser Ala Lys Ala Ile Ile Val Tyr Thr Gln Thr
370 375 380

Gly Gly Ser Pro Met Phe Leu Ser Lys Tyr Arg Pro Tyr Leu Pro Ile
385 390 395 400

Ile Ala Val Thr Pro Asn Arg Asn Val Tyr Tyr Arg Leu Ala Val Glu
405 410 415

Trp Gly Val Tyr Pro Met Leu Thr Ser Glu Ser Asn Arg Thr Val Trp
420 425 430

Arg His Gln Ala Cys Val Tyr Gly Val Glu Lys Gly Ile Leu Ser Asn
435 440 445

Tyr Asp Lys Ile Leu Val Phe Ser Arg Gly Ala Gly Met Gln Asp Thr
450 455 460

Asn Asn Leu Thr Leu Thr Thr Val Asn Asp Val Leu Ser Pro Ser Leu
465 470 475 480

Glu

<210> 23
<211> 1662
<212> DNA
<213> Chlamydia trachomatis

<220>
<221> CDS
<222> (1)..(1662)
<223>

<400> 23
atg cga ata gga gat cct atg aac aaa ctc atc aga cga gct gtg acg 48
Met Arg Ile Gly Asp Pro Met Asn Lys Leu Ile Arg Arg Ala Val Thr

1 5 10 15

atc ttc gcg gtg act agt gtg gcg agt tta ttt gct agc ggg gtg tta 96
Ile Phe Ala Val Thr Ser Val Ala Ser Leu Phe Ala Ser Gly Val Leu
20 25 30

gag acc tct atg gca gag tct ctc tct acc aac gtt att agc tta gct 144
Glu Thr Ser Met Ala Glu Ser Leu Ser Thr Asn Val Ile Ser Leu Ala
35 40 45

gac acc aaa gcg aaa gag acc act tct cat caa aaa gac aga aaa gca 192
Asp Thr Lys Ala Lys Glu Thr Thr Ser His Gln Lys Asp Arg Lys Ala
50 55 60

aga aaa aat cat caa aat agg act tcc gta gtc cgt aaa gag gtt act 240
Arg Lys Asn His Gln Asn Arg Thr Ser Val Val Arg Lys Glu Val Thr
65 70 75 80

gca gtt cgt gat act aaa gct gta gag cct aga cag gat tct tgc ttt 288
Ala Val Arg Asp Thr Lys Ala Val Glu Pro Arg Gln Asp Ser Cys Phe
85 90 95

ggc aaa atg tat aca gtc aaa gtt aat gat gat cgt aat gta gaa atc 336
Gly Lys Met Tyr Thr Val Lys Val Asn Asp Asp Arg Asn Val Glu Ile
100 105 110

gtg cag tcc gtt cct gaa tat gct acg gta gga tct cca tat cct att 384
Val Gln Ser Val Pro Glu Tyr Ala Thr Val Gly Ser Pro Tyr Pro Ile
115 120 125

gag att act gct ata ggg aaa aga gac tgt gtt gat gta atc att aca 432
Glu Ile Thr Ala Ile Gly Lys Arg Asp Cys Val Asp Val Ile Ile Thr
130 135 140

cag caa tta cca tgc gaa gca gag ttt gtt agc agt gat cca gct act 480
Gln Gln Leu Pro Cys Glu Ala Glu Phe Val Ser Ser Asp Pro Ala Thr
145 150 155 160

act cct act gct gat ggt aag cta gtt tgg aaa att gat cgg tta gga 528
Thr Pro Thr Ala Asp Gly Lys Leu Val Trp Lys Ile Asp Arg Leu Gly
165 170 175

cag ggc gaa aag agt aaa att act gta tgg gta aaa cct ctt aaa gaa 576
Gln Gly Glu Lys Ser Lys Ile Thr Val Trp Val Lys Pro Leu Lys Glu
180 185 190

ggt tgc tgc ttt aca gct gca acg gtt tgt gct tgt cca gag atc cgt 624
Gly Cys Cys Phe Thr Ala Ala Thr Val Cys Ala Cys Pro Glu Ile Arg
195 200 205

tcg gtt acg aaa tgt ggc cag cct gct atc tgt gtt aaa cag gaa ggt 672
Ser Val Thr Lys Cys Gly Gln Pro Ala Ile Cys Val Lys Gln Glu Gly
210 215 220

cca gaa agc gca tgt ttg cgt tgc cca gta act tat aga att aat gta 720
Pro Glu Ser Ala Cys Leu Arg Cys Pro Val Thr Tyr Arg Ile Asn Val
225 230 235 240

```
gtc aac caa gga aca gca aca gca cgt aat gtt gtt gtg gaa aat cct      768
Val Asn Gln Gly Thr Ala Thr Ala Arg Asn Val Val Val Glu Asn Pro
                245                 250                 255

gtt cca gat ggc tat gct cat gca tcc gga cag cgt gta ttg aca tat      816
Val Pro Asp Gly Tyr Ala His Ala Ser Gly Gln Arg Val Leu Thr Tyr
            260                 265                 270

act ctt ggg gat atg caa cct gga gaa cag aga aca atc acc gtg gag      864
Thr Leu Gly Asp Met Gln Pro Gly Glu Gln Arg Thr Ile Thr Val Glu
        275                 280                 285

ttt tgt ccg ctt aaa cgt ggt cga gtc aca aat att gct aca gtt tct      912
Phe Cys Pro Leu Lys Arg Gly Arg Val Thr Asn Ile Ala Thr Val Ser
    290                 295                 300

tac tgt ggt gga cac aaa aat act gct agc gta aca aca gtg atc aat      960
Tyr Cys Gly Gly His Lys Asn Thr Ala Ser Val Thr Thr Val Ile Asn
305                 310                 315                 320

gag cct tgc gtg caa gtt aac atc gag gga gca gat tgg tct tat gtt     1008
Glu Pro Cys Val Gln Val Asn Ile Glu Gly Ala Asp Trp Ser Tyr Val
                325                 330                 335

tgt aag cct gta gaa tat gtt atc tct gtt tct aac cct ggt gac tta     1056
Cys Lys Pro Val Glu Tyr Val Ile Ser Val Ser Asn Pro Gly Asp Leu
            340                 345                 350

gtt tta cga gac gtt gta att gaa gat acg ctt tct cct gga ata act     1104
Val Leu Arg Asp Val Val Ile Glu Asp Thr Leu Ser Pro Gly Ile Thr
        355                 360                 365

gtt gtt gaa gca gct gga gct cag att tct tgt aat aaa ttg gtt tgg     1152
Val Val Glu Ala Ala Gly Ala Gln Ile Ser Cys Asn Lys Leu Val Trp
    370                 375                 380

act ttg aag gaa ctc aat cct gga gag tct tta caa tat aag gtt cta     1200
Thr Leu Lys Glu Leu Asn Pro Gly Glu Ser Leu Gln Tyr Lys Val Leu
385                 390                 395                 400

gta aga gct caa act cca ggg caa ttc aca aac aac gtt gtt gtg aaa     1248
Val Arg Ala Gln Thr Pro Gly Gln Phe Thr Asn Asn Val Val Val Lys
                405                 410                 415

agt tgc tct gat tgc ggt att tgt act tct tgc gca gaa gca aca act     1296
Ser Cys Ser Asp Cys Gly Ile Cys Thr Ser Cys Ala Glu Ala Thr Thr
            420                 425                 430

tac tgg aaa gga gtt gct gct act cat atg tgc gta gta gat act tgt     1344
Tyr Trp Lys Gly Val Ala Ala Thr His Met Cys Val Val Asp Thr Cys
        435                 440                 445

gat cct att tgc gta gga gag aac act gtt tat cgt atc tgt gtg aca     1392
Asp Pro Ile Cys Val Gly Glu Asn Thr Val Tyr Arg Ile Cys Val Thr
    450                 455                 460

aac aga ggt tct gct gaa gat aca aat gtg tcc tta att ttg aaa ttc     1440
Asn Arg Gly Ser Ala Glu Asp Thr Asn Val Ser Leu Ile Leu Lys Phe
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465 470 475 480

tct aaa gaa tta caa cct ata tct ttc tct gga cca act aaa gga acc 1488
Ser Lys Glu Leu Gln Pro Ile Ser Phe Ser Gly Pro Thr Lys Gly Thr
485 490 495

att aca gga aac acg gta gtg ttt gat tcg tta cct aga tta ggt tct 1536
Ile Thr Gly Asn Thr Val Val Phe Asp Ser Leu Pro Arg Leu Gly Ser
500 505 510

aaa gaa act gta gag ttt tct gta acg ttg aaa gca gta tcc gct gga 1584
Lys Glu Thr Val Glu Phe Ser Val Thr Leu Lys Ala Val Ser Ala Gly
515 520 525

gat gct cgt ggg gaa gct att ctt tct tcc gat aca ttg aca gtt cct 1632
Asp Ala Arg Gly Glu Ala Ile Leu Ser Ser Asp Thr Leu Thr Val Pro
530 535 540

gta tct gat acg gag aat aca cat atc tat 1662
Val Ser Asp Thr Glu Asn Thr His Ile Tyr
545 550

<210> 24
<211> 554
<212> PRT
<213> Chlamydia trachomatis

<400> 24

Met Arg Ile Gly Asp Pro Met Asn Lys Leu Ile Arg Arg Ala Val Thr
1 5 10 15

Ile Phe Ala Val Thr Ser Val Ala Ser Leu Phe Ala Ser Gly Val Leu
20 25 30

Glu Thr Ser Met Ala Glu Ser Leu Ser Thr Asn Val Ile Ser Leu Ala
35 40 45

Asp Thr Lys Ala Lys Glu Thr Thr Ser His Gln Lys Asp Arg Lys Ala
50 55 60

Arg Lys Asn His Gln Asn Arg Thr Ser Val Val Arg Lys Glu Val Thr
65 70 75 80

Ala Val Arg Asp Thr Lys Ala Val Glu Pro Arg Gln Asp Ser Cys Phe
85 90 95

Gly Lys Met Tyr Thr Val Lys Val Asn Asp Asp Arg Asn Val Glu Ile
100 105 110

Val Gln Ser Val Pro Glu Tyr Ala Thr Val Gly Ser Pro Tyr Pro Ile
115 120 125

Glu Ile Thr Ala Ile Gly Lys Arg Asp Cys Val Asp Val Ile Ile Thr
130 135 140

Gln Gln Leu Pro Cys Glu Ala Glu Phe Val Ser Ser Asp Pro Ala Thr
145 150 155 160

Thr Pro Thr Ala Asp Gly Lys Leu Val Trp Lys Ile Asp Arg Leu Gly
165 170 175

Gln Gly Glu Lys Ser Lys Ile Thr Val Trp Val Lys Pro Leu Lys Glu
180 185 190

Gly Cys Cys Phe Thr Ala Ala Thr Val Cys Ala Cys Pro Glu Ile Arg
195 200 205

Ser Val Thr Lys Cys Gly Gln Pro Ala Ile Cys Val Lys Gln Glu Gly
210 215 220

Pro Glu Ser Ala Cys Leu Arg Cys Pro Val Thr Tyr Arg Ile Asn Val
225 230 235 240

Val Asn Gln Gly Thr Ala Thr Ala Arg Asn Val Val Val Glu Asn Pro
245 250 255

Val Pro Asp Gly Tyr Ala His Ala Ser Gly Gln Arg Val Leu Thr Tyr
260 265 270

Thr Leu Gly Asp Met Gln Pro Gly Glu Gln Arg Thr Ile Thr Val Glu
275 280 285

Phe Cys Pro Leu Lys Arg Gly Arg Val Thr Asn Ile Ala Thr Val Ser
290 295 300

Tyr Cys Gly Gly His Lys Asn Thr Ala Ser Val Thr Thr Val Ile Asn
305 310 315 320

Glu Pro Cys Val Gln Val Asn Ile Glu Gly Ala Asp Trp Ser Tyr Val
325 330 335

Cys Lys Pro Val Glu Tyr Val Ile Ser Val Ser Asn Pro Gly Asp Leu
340 345 350

Val Leu Arg Asp Val Val Ile Glu Asp Thr Leu Ser Pro Gly Ile Thr
355 360 365

Val Val Glu Ala Ala Gly Ala Gln Ile Ser Cys Asn Lys Leu Val Trp
370 375 380

Thr Leu Lys Glu Leu Asn Pro Gly Glu Ser Leu Gln Tyr Lys Val Leu
385 390 395 400

Val Arg Ala Gln Thr Pro Gly Gln Phe Thr Asn Asn Val Val Val Lys
405 410 415

Ser Cys Ser Asp Cys Gly Ile Cys Thr Ser Cys Ala Glu Ala Thr Thr
420 425 430

Tyr Trp Lys Gly Val Ala Ala Thr His Met Cys Val Val Asp Thr Cys
435 440 445

Asp Pro Ile Cys Val Gly Glu Asn Thr Val Tyr Arg Ile Cys Val Thr
450 455 460

Asn Arg Gly Ser Ala Glu Asp Thr Asn Val Ser Leu Ile Leu Lys Phe
465 470 475 480

Ser Lys Glu Leu Gln Pro Ile Ser Phe Ser Gly Pro Thr Lys Gly Thr
485 490 495

Ile Thr Gly Asn Thr Val Val Phe Asp Ser Leu Pro Arg Leu Gly Ser
500 505 510

Lys Glu Thr Val Glu Phe Ser Val Thr Leu Lys Ala Val Ser Ala Gly
515 520 525

Asp Ala Arg Gly Glu Ala Ile Leu Ser Ser Asp Thr Leu Thr Val Pro
530 535 540

Val Ser Asp Thr Glu Asn Thr His Ile Tyr
545 550

<210> 25
<211> 729
<212> DNA
<213> Chlamydia trachomatis

<220>
<221> CDS
<222> (1)..(729)
<223>

<400> 25
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atg aat cgt aga aac acg atg att gta gca gct tct gtg aat gca gta      48
Met Asn Arg Arg Asn Thr Met Ile Val Ala Ala Ser Val Asn Ala Val
1               5                   10                  15

ctc ttg gca gtg ctg ttt atg aca gca cgc tat tca gag caa gag gta      96
Leu Leu Ala Val Leu Phe Met Thr Ala Arg Tyr Ser Glu Gln Glu Val
            20                  25                  30

gag tat tcg cag aaa ata gca cct att aaa att tta gag ccg gta cca     144
Glu Tyr Ser Gln Lys Ile Ala Pro Ile Lys Ile Leu Glu Pro Val Pro
        35                  40                  45

gtt gtt gag aag gct cct gaa aaa tta gaa aaa aat cca gaa gtg atc     192
Val Val Glu Lys Ala Pro Glu Lys Leu Glu Lys Asn Pro Glu Val Ile
    50                  55                  60

gct aag ccc gca cag gtt gtg aga aat cct gta gtc tct aaa gcg gag     240
Ala Lys Pro Ala Gln Val Val Arg Asn Pro Val Val Ser Lys Ala Glu
65                  70                  75                  80

ctt gct gcg caa ttc aca gat aaa aat caa act gtt gag aaa gag atc     288
Leu Ala Ala Gln Phe Thr Asp Lys Asn Gln Thr Val Glu Lys Glu Ile
                85                  90                  95

aaa gtc tct cct aaa gcg acg cct cct cct gtg gtt gtt gaa tct cct     336
Lys Val Ser Pro Lys Ala Thr Pro Pro Pro Val Val Val Glu Ser Pro
            100                 105                 110

aca tcc gaa att cct gtt gtg cag gaa aaa agt gca gac aaa cct gca     384
Thr Ser Glu Ile Pro Val Val Gln Glu Lys Ser Ala Asp Lys Pro Ala
        115                 120                 125

gag caa gaa gaa ttt tct aca gtt att gtt aag aag gga gat ttt tta     432
Glu Gln Glu Glu Phe Ser Thr Val Ile Val Lys Lys Gly Asp Phe Leu
    130                 135                 140

gag cga att gct aga tcc cat cac act aca gtt tct gca ttg atg caa     480
Glu Arg Ile Ala Arg Ser His His Thr Thr Val Ser Ala Leu Met Gln
145                 150                 155                 160

ctt aat gat ttg tcg tcg acg caa tta caa ata gga caa gtt tta cgc     528
Leu Asn Asp Leu Ser Ser Thr Gln Leu Gln Ile Gly Gln Val Leu Arg
                165                 170                 175

gtt cct aaa acg aat aag aca gag aaa gat ctt caa gtt aag acc ccc     576
Val Pro Lys Thr Asn Lys Thr Glu Lys Asp Leu Gln Val Lys Thr Pro
            180                 185                 190

aat cca gaa gat tat tat gtg att aaa gaa ggg gat agt cct tgg gct     624
Asn Pro Glu Asp Tyr Tyr Val Ile Lys Glu Gly Asp Ser Pro Trp Ala
```

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        195                 200                 205

ata gct ttg agt aat ggg att cga tta gat gaa ttg ttg aaa ttg aat       672
Ile Ala Leu Ser Asn Gly Ile Arg Leu Asp Glu Leu Leu Lys Leu Asn
    210                 215                 220

gga tta gat gag cag aaa gct cgt aag ttg cgt cct gga gat aga tta       720
Gly Leu Asp Glu Gln Lys Ala Arg Lys Leu Arg Pro Gly Asp Arg Leu
225                 230                 235                     240

cga att cga                                                           729
Arg Ile Arg


<210>  26
<211>  243
<212>  PRT
<213>  Chlamydia trachomatis

<400>  26

Met Asn Arg Arg Asn Thr Met Ile Val Ala Ala Ser Val Asn Ala Val
1               5                   10                  15

Leu Leu Ala Val Leu Phe Met Thr Ala Arg Tyr Ser Glu Gln Glu Val
            20                  25                  30

Glu Tyr Ser Gln Lys Ile Ala Pro Ile Lys Ile Leu Glu Pro Val Pro
        35                  40                  45

Val Val Glu Lys Ala Pro Glu Lys Leu Glu Lys Asn Pro Glu Val Ile
    50                  55                  60

Ala Lys Pro Ala Gln Val Val Arg Asn Pro Val Val Ser Lys Ala Glu
65                  70                  75                  80

Leu Ala Ala Gln Phe Thr Asp Lys Asn Gln Thr Val Glu Lys Glu Ile
                85                  90                  95

Lys Val Ser Pro Lys Ala Thr Pro Pro Pro Val Val Val Glu Ser Pro
            100                 105                 110

Thr Ser Glu Ile Pro Val Val Gln Glu Lys Ser Ala Asp Lys Pro Ala
        115                 120                 125

Glu Gln Glu Glu Phe Ser Thr Val Ile Val Lys Lys Gly Asp Phe Leu
    130                 135                 140
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Glu Arg Ile Ala Arg Ser His His Thr Thr Val Ser Ala Leu Met Gln
145 150 155 160

Leu Asn Asp Leu Ser Ser Thr Gln Leu Gln Ile Gly Gln Val Leu Arg
165 170 175

Val Pro Lys Thr Asn Lys Thr Glu Lys Asp Leu Gln Val Lys Thr Pro
180 185 190

Asn Pro Glu Asp Tyr Tyr Val Ile Lys Glu Gly Asp Ser Pro Trp Ala
195 200 205

Ile Ala Leu Ser Asn Gly Ile Arg Leu Asp Glu Leu Leu Lys Leu Asn
210 215 220

Gly Leu Asp Glu Gln Lys Ala Arg Lys Leu Arg Pro Gly Asp Arg Leu
225 230 235 240

Arg Ile Arg

<210> 27
<211> 1167
<212> DNA
<213> Chlamydia pneumoniae

<220>
<221> CDS
<222> (1)..(1167)
<223>

<400> 27
atg aaa aaa ctc tta aag tcg gcg tta tta tcc gcc gca ttt gct ggt 48
Met Lys Lys Leu Leu Lys Ser Ala Leu Leu Ser Ala Ala Phe Ala Gly
1 5 10 15

tct gtc ggc tcc tta caa gcc ttg cct gta ggg aac cct tct gat cca 96
Ser Val Gly Ser Leu Gln Ala Leu Pro Val Gly Asn Pro Ser Asp Pro
20 25 30

agc tta tta att gat ggt aca ata tgg gaa ggt gct gca gga gat cct 144
Ser Leu Leu Ile Asp Gly Thr Ile Trp Glu Gly Ala Ala Gly Asp Pro
35 40 45

tgc gat cct tgc gct act tgg tgc gac gct att agc tta cgt gct gga 192
Cys Asp Pro Cys Ala Thr Trp Cys Asp Ala Ile Ser Leu Arg Ala Gly
50 55 60

ttt tac gga gac tat gtt ttc gac cgt atc tta aaa gta gat gca cct 240
Phe Tyr Gly Asp Tyr Val Phe Asp Arg Ile Leu Lys Val Asp Ala Pro

65 70 75 80

aaa aca ttt tct atg gga gcc aag cct act gga tcc gct gct gca aac 288
Lys Thr Phe Ser Met Gly Ala Lys Pro Thr Gly Ser Ala Ala Ala Asn
85 90 95

tat act act gcc gta gat aga cct aac ccg gcc tac aat aag cat tta 336
Tyr Thr Thr Ala Val Asp Arg Pro Asn Pro Ala Tyr Asn Lys His Leu
100 105 110

cac gat gca gag tgg ttc act aat gca ggc ttc att gcc tta aac att 384
His Asp Ala Glu Trp Phe Thr Asn Ala Gly Phe Ile Ala Leu Asn Ile
115 120 125

tgg gat cgc ttt gat gtt ttc tgt act tta gga gct tct aat ggt tac 432
Trp Asp Arg Phe Asp Val Phe Cys Thr Leu Gly Ala Ser Asn Gly Tyr
130 135 140

att aga gga aac tct aca gcg ttc aat ctc gtt ggt tta ttc gga gtt 480
Ile Arg Gly Asn Ser Thr Ala Phe Asn Leu Val Gly Leu Phe Gly Val
145 150 155 160

aaa ggt act act gta aat gca aat gaa cta cca aac gtt tct tta agt 528
Lys Gly Thr Thr Val Asn Ala Asn Glu Leu Pro Asn Val Ser Leu Ser
165 170 175

aac gga gtt gtt gaa ctt tac aca gac acc tct ttc tct tgg agc gta 576
Asn Gly Val Val Glu Leu Tyr Thr Asp Thr Ser Phe Ser Trp Ser Val
180 185 190

ggc gct cgt gga gcc tta tgg gaa tgc ggt tgt gca act ttg gga gct 624
Gly Ala Arg Gly Ala Leu Trp Glu Cys Gly Cys Ala Thr Leu Gly Ala
195 200 205

gaa ttc caa tat gca cag tcc aaa cct aaa gtt gaa gaa ctt aat gtg 672
Glu Phe Gln Tyr Ala Gln Ser Lys Pro Lys Val Glu Glu Leu Asn Val
210 215 220

atc tgt aac gta tcg caa ttc tct gta aac aaa ccc aag ggc tat aaa 720
Ile Cys Asn Val Ser Gln Phe Ser Val Asn Lys Pro Lys Gly Tyr Lys
225 230 235 240

ggc gtt gct ttc ccc ttg cca aca gac gct ggc gta gca aca gct act 768
Gly Val Ala Phe Pro Leu Pro Thr Asp Ala Gly Val Ala Thr Ala Thr
245 250 255

gga aca aag tct gcg acc atc aat tat cat gaa tgg caa gta gga gcc 816
Gly Thr Lys Ser Ala Thr Ile Asn Tyr His Glu Trp Gln Val Gly Ala
260 265 270

tct cta tct tac aga cta aac tct tta gtg cca tac att gga gta caa 864
Ser Leu Ser Tyr Arg Leu Asn Ser Leu Val Pro Tyr Ile Gly Val Gln
275 280 285

tgg tct cga gca act ttt gat gct gat aac atc cgc att gct cag cca 912
Trp Ser Arg Ala Thr Phe Asp Ala Asp Asn Ile Arg Ile Ala Gln Pro
290 295 300

aaa cta cct aca gct gtt tta aac tta act gca tgg aac cct tct tta 960
Lys Leu Pro Thr Ala Val Leu Asn Leu Thr Ala Trp Asn Pro Ser Leu
305 310 315 320

cta gga aat gcc aca gca ttg tct act act gat tcg ttc tca gac ttc 1008
Leu Gly Asn Ala Thr Ala Leu Ser Thr Thr Asp Ser Phe Ser Asp Phe
325 330 335

atg caa att gtt tcc tgt cag atc aac aag ttt aaa tct aga aaa gct 1056
Met Gln Ile Val Ser Cys Gln Ile Asn Lys Phe Lys Ser Arg Lys Ala
340 345 350

tgt gga gtt act gta gga gct act tta gtt gat gct gat aaa tgg tca 1104
Cys Gly Val Thr Val Gly Ala Thr Leu Val Asp Ala Asp Lys Trp Ser
355 360 365

ctt act gca gaa gct cgt tta att aac gag aga gct gct cac gta tct 1152
Leu Thr Ala Glu Ala Arg Leu Ile Asn Glu Arg Ala Ala His Val Ser
370 375 380

ggt cag ttc aga ttc 1167
Gly Gln Phe Arg Phe
385

<210> 28
<211> 389
<212> PRT
<213> Chlamydia pneumoniae

<400> 28

Met Lys Lys Leu Leu Lys Ser Ala Leu Leu Ser Ala Ala Phe Ala Gly
1 5 10 15

Ser Val Gly Ser Leu Gln Ala Leu Pro Val Gly Asn Pro Ser Asp Pro
20 25 30

Ser Leu Leu Ile Asp Gly Thr Ile Trp Glu Gly Ala Ala Gly Asp Pro
35 40 45

Cys Asp Pro Cys Ala Thr Trp Cys Asp Ala Ile Ser Leu Arg Ala Gly
50 55 60

Phe Tyr Gly Asp Tyr Val Phe Asp Arg Ile Leu Lys Val Asp Ala Pro
65 70 75 80

Lys Thr Phe Ser Met Gly Ala Lys Pro Thr Gly Ser Ala Ala Ala Asn
85 90 95

Tyr Thr Thr Ala Val Asp Arg Pro Asn Pro Ala Tyr Asn Lys His Leu
100 105 110

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His Asp Ala Glu Trp Phe Thr Asn Ala Gly Phe Ile Ala Leu Asn Ile
        115                 120                 125

Trp Asp Arg Phe Asp Val Phe Cys Thr Leu Gly Ala Ser Asn Gly Tyr
    130                 135                 140

Ile Arg Gly Asn Ser Thr Ala Phe Asn Leu Val Gly Leu Phe Gly Val
145                 150                 155                 160

Lys Gly Thr Thr Val Asn Ala Asn Glu Leu Pro Asn Val Ser Leu Ser
                165                 170                 175

Asn Gly Val Val Glu Leu Tyr Thr Asp Thr Ser Phe Ser Trp Ser Val
            180                 185                 190

Gly Ala Arg Gly Ala Leu Trp Glu Cys Gly Cys Ala Thr Leu Gly Ala
        195                 200                 205

Glu Phe Gln Tyr Ala Gln Ser Lys Pro Lys Val Glu Glu Leu Asn Val
    210                 215                 220

Ile Cys Asn Val Ser Gln Phe Ser Val Asn Lys Pro Lys Gly Tyr Lys
225                 230                 235                 240

Gly Val Ala Phe Pro Leu Pro Thr Asp Ala Gly Val Ala Thr Ala Thr
                245                 250                 255

Gly Thr Lys Ser Ala Thr Ile Asn Tyr His Glu Trp Gln Val Gly Ala
            260                 265                 270

Ser Leu Ser Tyr Arg Leu Asn Ser Leu Val Pro Tyr Ile Gly Val Gln
        275                 280                 285

Trp Ser Arg Ala Thr Phe Asp Ala Asp Asn Ile Arg Ile Ala Gln Pro
    290                 295                 300

Lys Leu Pro Thr Ala Val Leu Asn Leu Thr Ala Trp Asn Pro Ser Leu
305                 310                 315                 320

Leu Gly Asn Ala Thr Ala Leu Ser Thr Thr Asp Ser Phe Ser Asp Phe
                325                 330                 335
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Met Gln Ile Val Ser Cys Gln Ile Asn Lys Phe Lys Ser Arg Lys Ala
340 345 350

Cys Gly Val Thr Val Gly Ala Thr Leu Val Asp Ala Asp Lys Trp Ser
355 360 365

Leu Thr Ala Glu Ala Arg Leu Ile Asn Glu Arg Ala Ala His Val Ser
370 375 380

Gly Gln Phe Arg Phe
385

<210> 29
<211> 1668
<212> DNA
<213> Chlamydia pneumoniae

<220>
<221> CDS
<222> (1)..(1668)
<223>

<400> 29
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Met Ser Lys Leu Ile Arg Arg Val Val Thr Val Leu Ala Leu Thr Ser
1 5 10 15

atg gcg agt tgc ttt gcc agc ggg ggt ata gag gcc gct gta gca gag 96
Met Ala Ser Cys Phe Ala Ser Gly Gly Ile Glu Ala Ala Val Ala Glu
20 25 30

tct ctg att act aag atc gtc gct agt gcg gaa aca aag cca gca cct 144
Ser Leu Ile Thr Lys Ile Val Ala Ser Ala Glu Thr Lys Pro Ala Pro
35 40 45

gtt cct atg aca gcg aag aag gtt aga ctt gtc cgt aga aat aaa caa 192
Val Pro Met Thr Ala Lys Lys Val Arg Leu Val Arg Arg Asn Lys Gln
50 55 60

cca gtt gaa caa aaa agc cgt ggt gct ttt tgt gat aaa gaa ttt tat 240
Pro Val Glu Gln Lys Ser Arg Gly Ala Phe Cys Asp Lys Glu Phe Tyr
65 70 75 80

ccc tgt gaa gag gga cga tgt caa cct gta gag gct cag caa gag tct 288
Pro Cys Glu Glu Gly Arg Cys Gln Pro Val Glu Ala Gln Gln Glu Ser
85 90 95

tgc tac gga aga ttg tat tct gta aaa gta aac gat gat tgc aac gta 336
Cys Tyr Gly Arg Leu Tyr Ser Val Lys Val Asn Asp Asp Cys Asn Val
100 105 110

gaa att tgc cag tcc gtt cca gaa tac gct act gta gga tct cct tac 384
Glu Ile Cys Gln Ser Val Pro Glu Tyr Ala Thr Val Gly Ser Pro Tyr

115 120 125

cct att gaa atc ctt gct ata ggc aaa aaa gat tgt gtt gat gtt gtg 432
Pro Ile Glu Ile Leu Ala Ile Gly Lys Lys Asp Cys Val Asp Val Val
130 135 140

att aca caa cag cta cct tgc gaa gct gaa ttc gta agc agt gat cca 480
Ile Thr Gln Gln Leu Pro Cys Glu Ala Glu Phe Val Ser Ser Asp Pro
145 150 155 160

gaa aca act cct aca agt gat ggg aaa tta gtc tgg aaa atc gat cgc 528
Glu Thr Thr Pro Thr Ser Asp Gly Lys Leu Val Trp Lys Ile Asp Arg
165 170 175

ctg ggt gca gga gat aaa tgc aaa att act gta tgg gta aaa cct ctt 576
Leu Gly Ala Gly Asp Lys Cys Lys Ile Thr Val Trp Val Lys Pro Leu
180 185 190

aaa gaa ggt tgc tgc ttc aca gct gct act gta tgt gct tgc cca gag 624
Lys Glu Gly Cys Cys Phe Thr Ala Ala Thr Val Cys Ala Cys Pro Glu
195 200 205

ctc cgt tct tat act aaa tgc ggt caa cca gcc att tgt att aag caa 672
Leu Arg Ser Tyr Thr Lys Cys Gly Gln Pro Ala Ile Cys Ile Lys Gln
210 215 220

gaa gga cct gac tgt gct tgc cta aga tgc cct gta tgc tac aaa atc 720
Glu Gly Pro Asp Cys Ala Cys Leu Arg Cys Pro Val Cys Tyr Lys Ile
225 230 235 240

gaa gta gtg aac aca gga tct gct att gcc cgt aac gta act gta gat 768
Glu Val Val Asn Thr Gly Ser Ala Ile Ala Arg Asn Val Thr Val Asp
245 250 255

aat cct gtt ccc gat ggc tat tct cat gca tct ggt caa aga gtt ctc 816
Asn Pro Val Pro Asp Gly Tyr Ser His Ala Ser Gly Gln Arg Val Leu
260 265 270

tct ttt aac tta gga gac atg aga cct ggc gat aaa aag gta ttt aca 864
Ser Phe Asn Leu Gly Asp Met Arg Pro Gly Asp Lys Lys Val Phe Thr
275 280 285

gtt gag ttc tgc cct caa aga aga ggt caa atc act aac gtt gct act 912
Val Glu Phe Cys Pro Gln Arg Arg Gly Gln Ile Thr Asn Val Ala Thr
290 295 300

gta act tac tgc ggt gga cac aaa tgt tct gca aat gta act aca gtt 960
Val Thr Tyr Cys Gly Gly His Lys Cys Ser Ala Asn Val Thr Thr Val
305 310 315 320

gtt aat gag cct tgt gta caa gta aat atc tct ggt gct gat tgg tct 1008
Val Asn Glu Pro Cys Val Gln Val Asn Ile Ser Gly Ala Asp Trp Ser
325 330 335

tac gta tgt aaa cct gtg gag tac tct atc tca gta tcg aat cct gga 1056
Tyr Val Cys Lys Pro Val Glu Tyr Ser Ile Ser Val Ser Asn Pro Gly
340 345 350

gac ttg gtt ctt cat gat gtc gtg atc caa gat aca ctc cct tct ggt 1104
Asp Leu Val Leu His Asp Val Val Ile Gln Asp Thr Leu Pro Ser Gly
355 360 365

gtt aca gta ctc gaa gct cct ggt gga gag atc tgc tgt aat aaa gtt 1152
Val Thr Val Leu Glu Ala Pro Gly Gly Glu Ile Cys Cys Asn Lys Val
370 375 380

gtt tgg cgt att aaa gaa atg tgc cca gga gaa acc ctc cag ttt aaa 1200
Val Trp Arg Ile Lys Glu Met Cys Pro Gly Glu Thr Leu Gln Phe Lys
385 390 395 400

ctt gta gtg aaa gct caa gtt cct gga aga ttc aca aat caa gtt gca 1248
Leu Val Val Lys Ala Gln Val Pro Gly Arg Phe Thr Asn Gln Val Ala
405 410 415

gta act agt gag tct aac tgc gga aca tgt aca tct tgc gca gaa aca 1296
Val Thr Ser Glu Ser Asn Cys Gly Thr Cys Thr Ser Cys Ala Glu Thr
420 425 430

aca aca cat tgg aaa ggt ctt gca gct acc cat atg tgc gta tta gac 1344
Thr Thr His Trp Lys Gly Leu Ala Ala Thr His Met Cys Val Leu Asp
435 440 445

aca aat gat cct atc tgt gta gga gaa aat act gtc tat cgt atc tgt 1392
Thr Asn Asp Pro Ile Cys Val Gly Glu Asn Thr Val Tyr Arg Ile Cys
450 455 460

gta act aac cgt ggt tct gct gaa gat act aac gta tct tta atc ttg 1440
Val Thr Asn Arg Gly Ser Ala Glu Asp Thr Asn Val Ser Leu Ile Leu
465 470 475 480

aag ttc tca aaa gaa ctt cag cca ata gct tct tca ggt cca act aaa 1488
Lys Phe Ser Lys Glu Leu Gln Pro Ile Ala Ser Ser Gly Pro Thr Lys
485 490 495

gga acg att tca ggt aat acc gtt gtt ttc gac gct tta cct aaa ctc 1536
Gly Thr Ile Ser Gly Asn Thr Val Val Phe Asp Ala Leu Pro Lys Leu
500 505 510

ggt tct aag gaa tct gta gag ttt tct gtt acc ttg aaa ggt att gct 1584
Gly Ser Lys Glu Ser Val Glu Phe Ser Val Thr Leu Lys Gly Ile Ala
515 520 525

ccc gga gat gct cgc ggc gaa gct att ctt tct tct gat aca ctg act 1632
Pro Gly Asp Ala Arg Gly Glu Ala Ile Leu Ser Ser Asp Thr Leu Thr
530 535 540

tca cca gta tca gac aca gaa aat acc cac gtg tat 1668
Ser Pro Val Ser Asp Thr Glu Asn Thr His Val Tyr
545 550 555

<210> 30
<211> 556
<212> PRT
<213> Chlamydia pneumoniae

<400> 30

Met Ser Lys Leu Ile Arg Arg Val Val Thr Val Leu Ala Leu Thr Ser
1   5   10   15

Met Ala Ser Cys Phe Ala Ser Gly Gly Ile Glu Ala Ala Val Ala Glu
            20   25   30

Ser Leu Ile Thr Lys Ile Val Ala Ser Ala Glu Thr Lys Pro Ala Pro
        35   40   45

Val Pro Met Thr Ala Lys Lys Val Arg Leu Val Arg Arg Asn Lys Gln
    50   55   60

Pro Val Glu Gln Lys Ser Arg Gly Ala Phe Cys Asp Lys Glu Phe Tyr
65   70   75   80

Pro Cys Glu Glu Gly Arg Cys Gln Pro Val Glu Ala Gln Gln Glu Ser
                85   90   95

Cys Tyr Gly Arg Leu Tyr Ser Val Lys Val Asn Asp Asp Cys Asn Val
            100   105   110

Glu Ile Cys Gln Ser Val Pro Glu Tyr Ala Thr Val Gly Ser Pro Tyr
        115   120   125

Pro Ile Glu Ile Leu Ala Ile Gly Lys Lys Asp Cys Val Asp Val Val
    130   135   140

Ile Thr Gln Gln Leu Pro Cys Glu Ala Glu Phe Val Ser Ser Asp Pro
145   150   155   160

Glu Thr Thr Pro Thr Ser Asp Gly Lys Leu Val Trp Lys Ile Asp Arg
                165   170   175

Leu Gly Ala Gly Asp Lys Cys Lys Ile Thr Val Trp Val Lys Pro Leu
            180   185   190

Lys Glu Gly Cys Cys Phe Thr Ala Ala Thr Val Cys Ala Cys Pro Glu
        195   200   205

Leu Arg Ser Tyr Thr Lys Cys Gly Gln Pro Ala Ile Cys Ile Lys Gln
    210   215   220

Glu Gly Pro Asp Cys Ala Cys Leu Arg Cys Pro Val Cys Tyr Lys Ile
225 230 235 240

Glu Val Val Asn Thr Gly Ser Ala Ile Ala Arg Asn Val Thr Val Asp
245 250 255

Asn Pro Val Pro Asp Gly Tyr Ser His Ala Ser Gly Gln Arg Val Leu
260 265 270

Ser Phe Asn Leu Gly Asp Met Arg Pro Gly Asp Lys Lys Val Phe Thr
275 280 285

Val Glu Phe Cys Pro Gln Arg Arg Gly Gln Ile Thr Asn Val Ala Thr
290 295 300

Val Thr Tyr Cys Gly Gly His Lys Cys Ser Ala Asn Val Thr Thr Val
305 310 315 320

Val Asn Glu Pro Cys Val Gln Val Asn Ile Ser Gly Ala Asp Trp Ser
325 330 335

Tyr Val Cys Lys Pro Val Glu Tyr Ser Ile Ser Val Ser Asn Pro Gly
340 345 350

Asp Leu Val Leu His Asp Val Val Ile Gln Asp Thr Leu Pro Ser Gly
355 360 365

Val Thr Val Leu Glu Ala Pro Gly Gly Glu Ile Cys Cys Asn Lys Val
370 375 380

Val Trp Arg Ile Lys Glu Met Cys Pro Gly Glu Thr Leu Gln Phe Lys
385 390 395 400

Leu Val Val Lys Ala Gln Val Pro Gly Arg Phe Thr Asn Gln Val Ala
405 410 415

Val Thr Ser Glu Ser Asn Cys Gly Thr Cys Thr Ser Cys Ala Glu Thr
420 425 430

Thr Thr His Trp Lys Gly Leu Ala Ala Thr His Met Cys Val Leu Asp
435 440 445

Thr Asn Asp Pro Ile Cys Val Gly Glu Asn Thr Val Tyr Arg Ile Cys
450 455 460

Val Thr Asn Arg Gly Ser Ala Glu Asp Thr Asn Val Ser Leu Ile Leu
465 470 475 480

Lys Phe Ser Lys Glu Leu Gln Pro Ile Ala Ser Ser Gly Pro Thr Lys
485 490 495

Gly Thr Ile Ser Gly Asn Thr Val Val Phe Asp Ala Leu Pro Lys Leu
500 505 510

Gly Ser Lys Glu Ser Val Glu Phe Ser Val Thr Leu Lys Gly Ile Ala
515 520 525

Pro Gly Asp Ala Arg Gly Glu Ala Ile Leu Ser Ser Asp Thr Leu Thr
530 535 540

Ser Pro Val Ser Asp Thr Glu Asn Thr His Val Tyr
545 550 555

<210> 31
<211> 1452
<212> DNA
<213> Chlamydia pneumoniae

<220>
<221> CDS
<222> (1)..(1452)
<223>

<400> 31
atg atc aca cgc act aaa att att tgc act ata ggg cca gca acg aat 48
Met Ile Thr Arg Thr Lys Ile Ile Cys Thr Ile Gly Pro Ala Thr Asn
1 5 10 15

agt cca gag atg tta gca aaa ctt cta gat gct ggg atg aac gta gca 96
Ser Pro Glu Met Leu Ala Lys Leu Leu Asp Ala Gly Met Asn Val Ala
20 25 30

aga tta aat ttc agt cat ggg agt cac gaa act cat gga cag gct att 144
Arg Leu Asn Phe Ser His Gly Ser His Glu Thr His Gly Gln Ala Ile
35 40 45

gga ttt ctc aag gag tta agg gag cag aag cgg gtt cct tta gca att 192
Gly Phe Leu Lys Glu Leu Arg Glu Gln Lys Arg Val Pro Leu Ala Ile
50 55 60

atg cta gat act aag ggg cct gaa att cgt tta ggg aat att cct cag 240
Met Leu Asp Thr Lys Gly Pro Glu Ile Arg Leu Gly Asn Ile Pro Gln
65 70 75 80

cca att tcg gtt tct cag gga caa aag ctt cgt ctg gta agt agt gat 288
Pro Ile Ser Val Ser Gln Gly Gln Lys Leu Arg Leu Val Ser Ser Asp
85 90 95

atc gat ggg agt gct gaa ggg gga gtg tct ctc tat cct aag ggg ata 336
Ile Asp Gly Ser Ala Glu Gly Gly Val Ser Leu Tyr Pro Lys Gly Ile
100 105 110

ttt ccc ttt gtt cct gag ggt gct gat gtt tta ata gat gat ggc tac 384
Phe Pro Phe Val Pro Glu Gly Ala Asp Val Leu Ile Asp Asp Gly Tyr
115 120 125

att cat gct gtt gtt gtc tct tca gag gct gat tct tta gaa tta gag 432
Ile His Ala Val Val Val Ser Ser Glu Ala Asp Ser Leu Glu Leu Glu
130 135 140

ttt atg aac agt ggc ctt ctc aag tct cat aaa tct ttg agt atc cga 480
Phe Met Asn Ser Gly Leu Leu Lys Ser His Lys Ser Leu Ser Ile Arg
145 150 155 160

ggt gtt gat gtt gct ctt ccc ttt atg aca gag aaa gat att gcg gat 528
Gly Val Asp Val Ala Leu Pro Phe Met Thr Glu Lys Asp Ile Ala Asp
165 170 175

ctt aag ttt ggg gta gag cag aat atg gat gtg gtt gct gca tct ttt 576
Leu Lys Phe Gly Val Glu Gln Asn Met Asp Val Val Ala Ala Ser Phe
180 185 190

gtg cgc tac ggt gaa gat att gaa act atg cgc aag tgt tta gca gac 624
Val Arg Tyr Gly Glu Asp Ile Glu Thr Met Arg Lys Cys Leu Ala Asp
195 200 205

tta ggc aat cct aag atg ccc atc att gca aaa ata gaa aat cgt tta 672
Leu Gly Asn Pro Lys Met Pro Ile Ile Ala Lys Ile Glu Asn Arg Leu
210 215 220

ggg gta gaa aat ttc tct aag att gcc aag ctt gcg gat gga att atg 720
Gly Val Glu Asn Phe Ser Lys Ile Ala Lys Leu Ala Asp Gly Ile Met
225 230 235 240

att gct aga gga gat tta gga atc gag ctt tct gtc gtt gaa gtc cca 768
Ile Ala Arg Gly Asp Leu Gly Ile Glu Leu Ser Val Val Glu Val Pro
245 250 255

aat ttg caa aag atg atg gct aag gtt tct aga gaa aca ggt cac ttc 816
Asn Leu Gln Lys Met Met Ala Lys Val Ser Arg Glu Thr Gly His Phe
260 265 270

tgt gtg act gca acg cag atg cta gaa tct atg att cgc aat gtc tta 864
Cys Val Thr Ala Thr Gln Met Leu Glu Ser Met Ile Arg Asn Val Leu
275 280 285

cct aca cga gct gaa gtc tct gat att gcc aat gca att tat gat ggt 912
Pro Thr Arg Ala Glu Val Ser Asp Ile Ala Asn Ala Ile Tyr Asp Gly
290 295 300

tct tca gca gtg atg ttg tca ggg gaa act gca tct gga gcc cat ccc 960
Ser Ser Ala Val Met Leu Ser Gly Glu Thr Ala Ser Gly Ala His Pro

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305                 310                 315                 320

gtg gct gcc gtg aaa atc atg cgt tct gtg att tta gaa aca gaa aag      1008
Val Ala Ala Val Lys Ile Met Arg Ser Val Ile Leu Glu Thr Glu Lys
                325                 330                 335

aat ctc tcc cat gat tca ttc tta aaa tta gac gat agc aat agc gct      1056
Asn Leu Ser His Asp Ser Phe Leu Lys Leu Asp Asp Ser Asn Ser Ala
            340                 345                 350

ctt cag gtg tcc ccc tat ctc tca gcc att gga ttg gca ggc att cag      1104
Leu Gln Val Ser Pro Tyr Leu Ser Ala Ile Gly Leu Ala Gly Ile Gln
        355                 360                 365

att gca gaa agg gca gac gcc aaa gct ctt att gtt tat aca gaa tca      1152
Ile Ala Glu Arg Ala Asp Ala Lys Ala Leu Ile Val Tyr Thr Glu Ser
    370                 375                 380

gga agt tct ccg atg ttt ctc tct aaa tat cgt ccg aaa ttc cct atc      1200
Gly Ser Ser Pro Met Phe Leu Ser Lys Tyr Arg Pro Lys Phe Pro Ile
385                 390                 395                 400

att gcc gtg act cca agc act tct gtt tac tat cgc cta gct ttg gaa      1248
Ile Ala Val Thr Pro Ser Thr Ser Val Tyr Tyr Arg Leu Ala Leu Glu
                405                 410                 415

tgg ggg gtc tat cct atg ctt acc cag gaa agt gat cgc gct gta tgg      1296
Trp Gly Val Tyr Pro Met Leu Thr Gln Glu Ser Asp Arg Ala Val Trp
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aga cat cag gcc tgt att tat ggc ata gaa cag ggc att ctc tct aat      1344
Arg His Gln Ala Cys Ile Tyr Gly Ile Glu Gln Gly Ile Leu Ser Asn
        435                 440                 445

tat gat cgg att ctt gtg ctt agc aga gga gcc tgt atg gaa gaa aca      1392
Tyr Asp Arg Ile Leu Val Leu Ser Arg Gly Ala Cys Met Glu Glu Thr
    450                 455                 460

aat aat ctt acc ctg aca ata gtg aat gat att ttg act ggg tcg gaa      1440
Asn Asn Leu Thr Leu Thr Ile Val Asn Asp Ile Leu Thr Gly Ser Glu
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Arg Leu Asn Phe Ser His Gly Ser His Glu Thr His Gly Gln Ala Ile
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Gly Phe Leu Lys Glu Leu Arg Glu Gln Lys Arg Val Pro Leu Ala Ile
    50                  55                  60

Met Leu Asp Thr Lys Gly Pro Glu Ile Arg Leu Gly Asn Ile Pro Gln
65                  70                  75                  80

Pro Ile Ser Val Ser Gln Gly Gln Lys Leu Arg Leu Val Ser Ser Asp
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Ile Asp Gly Ser Ala Glu Gly Gly Val Ser Leu Tyr Pro Lys Gly Ile
            100                 105                 110

Phe Pro Phe Val Pro Glu Gly Ala Asp Val Leu Ile Asp Asp Gly Tyr
        115                 120                 125

Ile His Ala Val Val Val Ser Ser Glu Ala Asp Ser Leu Glu Leu Glu
    130                 135                 140

Phe Met Asn Ser Gly Leu Leu Lys Ser His Lys Ser Leu Ser Ile Arg
145                 150                 155                 160

Gly Val Asp Val Ala Leu Pro Phe Met Thr Glu Lys Asp Ile Ala Asp
                165                 170                 175

Leu Lys Phe Gly Val Glu Gln Asn Met Asp Val Val Ala Ala Ser Phe
            180                 185                 190

Val Arg Tyr Gly Glu Asp Ile Glu Thr Met Arg Lys Cys Leu Ala Asp
        195                 200                 205

Leu Gly Asn Pro Lys Met Pro Ile Ile Ala Lys Ile Glu Asn Arg Leu
    210                 215                 220

Gly Val Glu Asn Phe Ser Lys Ile Ala Lys Leu Ala Asp Gly Ile Met
225                 230                 235                 240

Ile Ala Arg Gly Asp Leu Gly Ile Glu Leu Ser Val Val Glu Val Pro
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Cys Val Thr Ala Thr Gln Met Leu Glu Ser Met Ile Arg Asn Val Leu
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Pro Thr Arg Ala Glu Val Ser Asp Ile Ala Asn Ala Ile Tyr Asp Gly
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Ser Ser Ala Val Met Leu Ser Gly Glu Thr Ala Ser Gly Ala His Pro
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Val Ala Ala Val Lys Ile Met Arg Ser Val Ile Leu Glu Thr Glu Lys
325 330 335

Asn Leu Ser His Asp Ser Phe Leu Lys Leu Asp Asp Ser Asn Ser Ala
340 345 350

Leu Gln Val Ser Pro Tyr Leu Ser Ala Ile Gly Leu Ala Gly Ile Gln
355 360 365

Ile Ala Glu Arg Ala Asp Ala Lys Ala Leu Ile Val Tyr Thr Glu Ser
370 375 380

Gly Ser Ser Pro Met Phe Leu Ser Lys Tyr Arg Pro Lys Phe Pro Ile
385 390 395 400

Ile Ala Val Thr Pro Ser Thr Ser Val Tyr Tyr Arg Leu Ala Leu Glu
405 410 415

Trp Gly Val Tyr Pro Met Leu Thr Gln Glu Ser Asp Arg Ala Val Trp
420 425 430

Arg His Gln Ala Cys Ile Tyr Gly Ile Glu Gln Gly Ile Leu Ser Asn
435 440 445

Tyr Asp Arg Ile Leu Val Leu Ser Arg Gly Ala Cys Met Glu Glu Thr
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gag gaa aga ggg gag atg gca ata gct cga gtc cag cag tgt gga tgg 144
Glu Glu Arg Gly Glu Met Ala Ile Ala Arg Val Gln Gln Cys Gly Trp
35 40 45

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Asn His Thr Ile Val Lys Val Ser Leu Ile Ile Leu Ala Leu Leu Thr
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gct ttg att tta tgt ctt tat gat tct cag ggc ctt cct gag gaa ctc 336
Ala Leu Ile Leu Cys Leu Tyr Asp Ser Gln Gly Leu Pro Glu Glu Leu
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130 135 140

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Val Arg Ser Glu Glu Gly Glu Lys Glu Ile Ser Arg Leu Gln Asp Leu
225                 230                 235                 240

atc agt ttg cag cag cag acg gtg caa gat tta agg agt cgg atc gat      768
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gac gag cag aag aga tgc tgg acg gct tta caa cgt att aac caa tct      816
Asp Glu Gln Lys Arg Cys Trp Thr Ala Leu Gln Arg Ile Asn Gln Ser
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cag aag gat ata caa cgg gct cat gat cgc gag gct tcg cag cgt gcc      864
Gln Lys Asp Ile Gln Arg Ala His Asp Arg Glu Ala Ser Gln Arg Ala
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tgt gag ggc aca gag atg gat tgt gca gaa cgc cag caa ctg gag aag      912
Cys Glu Gly Thr Glu Met Asp Cys Ala Glu Arg Gln Gln Leu Glu Lys
    290                 295                 300

gat tta agg aga cag ctg aaa tct atg cag gag tgg att gag atg agg      960
Asp Leu Arg Arg Gln Leu Lys Ser Met Gln Glu Trp Ile Glu Met Arg
305                 310                 315                 320

ggc aca atc cat caa caa gag aag gct tgg cgt aag cag aat gcc aaa     1008
Gly Thr Ile His Gln Gln Glu Lys Ala Trp Arg Lys Gln Asn Ala Lys
                325                 330                 335

tta gaa aga tta caa gag gat ctg aga ctt act ggg att gct ttt gac     1056
Leu Glu Arg Leu Gln Glu Asp Leu Arg Leu Thr Gly Ile Ala Phe Asp
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gaa caa tct ctg ttc tat cgc gaa tat aaa gag aaa tat ctg agt cag     1104
Glu Gln Ser Leu Phe Tyr Arg Glu Tyr Lys Glu Lys Tyr Leu Ser Gln
        355                 360                 365

aaa cta gat atg caa aag att tta cag gaa gtc aac gca gag aaa agt     1152
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    370                 375                 380

gag aag gct tgc tta gag agt ctg gtc cat gac tat gag aag cag ctc     1200
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385                 390                 395                 400
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gaa tta ggg aag cag caa cag gaa gac tac gaa caa acc caa gaa att      1296
Glu Leu Gly Lys Gln Gln Gln Glu Asp Tyr Glu Gln Thr Gln Glu Ile
            420                 425                 430

aga cgt ctg agt aca ttc att ctt gag tac cag gac agt ctg cgt gag      1344
Arg Arg Leu Ser Thr Phe Ile Leu Glu Tyr Gln Asp Ser Leu Arg Glu
        435                 440                 445

gca gaa aaa gtt gag aaa gat ttc caa gag cta caa caa agg tat agc      1392
Ala Glu Lys Val Glu Lys Asp Phe Gln Glu Leu Gln Gln Arg Tyr Ser
    450                 455                 460

cgt ctt caa gag gag aaa cag gta aaa gaa aaa atc tta gaa gaa agt      1440
Arg Leu Gln Glu Glu Lys Gln Val Lys Glu Lys Ile Leu Glu Glu Ser
465                 470                 475                 480

atg aat cat ttt gcc gat ctc ttt gag aag gct caa aag gaa aac atg      1488
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gcc tac aag aag aag tta gcg gat tta gag ggt gcc gct gct cct act      1536
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            500                 505                 510

gag atc ggt gag gac gat gac tgg gta ctc aca gat tct gct tct ctc      1584
Glu Ile Gly Glu Asp Asp Asp Trp Val Leu Thr Asp Ser Ala Ser Leu
        515                 520                 525

agc cag aag aag atc cgc gaa ctc gtg gaa gag aat caa gaa ctc ctg      1632
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aaa gca ctt gca ttt aaa tct aac gaa ttg act caa ctg gtt gcc gat      1680
Lys Ala Leu Ala Phe Lys Ser Asn Glu Leu Thr Gln Leu Val Ala Asp
545                 550                 555                 560

gct gta gaa gct gaa aaa gaa atc agc aag ctt cga gaa cac ata gaa      1728
Ala Val Glu Ala Glu Lys Glu Ile Ser Lys Leu Arg Glu His Ile Glu
                565                 570                 575

gag cag aaa gaa gga tta cga gct ctt gat aag atg cat gca caa gcg      1776
Glu Gln Lys Glu Gly Leu Arg Ala Leu Asp Lys Met His Ala Gln Ala
            580                 585                 590

atc aaa gat tgc gaa gct gct cag aga aaa tgc tgt gac ctt gag agc      1824
Ile Lys Asp Cys Glu Ala Ala Gln Arg Lys Cys Cys Asp Leu Glu Ser
        595                 600                 605

ctt ctc tct cct gtt cga gaa gat gct gga atg aga ttt gag cta gag      1872
Leu Leu Ser Pro Val Arg Glu Asp Ala Gly Met Arg Phe Glu Leu Glu
    610                 615                 620

gtc gag ctt caa aga ttg caa gaa gaa aat gca cag ctt aga gcg gag      1920
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35 40 45

Asn His Thr Ile Val Lys Val Ser Leu Ile Ile Leu Ala Leu Leu Thr
50 55 60

Ile Leu Gly Gly Gly Leu Leu Val Gly Leu Leu Pro Ala Val Pro Met
65 70 75 80

Phe Ile Gly Thr Gly Leu Ile Ala Leu Gly Ala Val Ile Phe Ala Leu
85 90 95

Ala Leu Ile Leu Cys Leu Tyr Asp Ser Gln Gly Leu Pro Glu Glu Leu
100 105 110

Pro Pro Val Pro Glu Pro Gln Gln Ile Gln Ile Glu Asp Leu Arg Asn
115 120 125

Glu Thr Arg Glu Val Leu Glu Gly Thr Leu Leu Glu Val Leu Leu Lys
130 135 140

Asp Arg Asp Ala Lys Asp Pro Ala Val Pro Gln Val Val Val Asp Cys
145 150 155 160

Glu Lys Arg Leu Gly Met Leu Asp Arg Lys Leu Arg Arg Glu Glu Glu
165 170 175

Ile Leu Tyr Arg Ser Thr Ala His Leu Lys Asp Glu Glu Arg Tyr Glu
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Phe Leu Leu Glu Leu Leu Glu Met Arg Ser Leu Val Ala Asp Arg Leu
195 200 205

Glu Phe Asn Arg Arg Ser Tyr Glu Arg Phe Val Gln Gly Ile Met Thr
210 215 220

Val Arg Ser Glu Glu Gly Glu Lys Glu Ile Ser Arg Leu Gln Asp Leu
225 230 235 240

Ile Ser Leu Gln Gln Gln Thr Val Gln Asp Leu Arg Ser Arg Ile Asp
245 250 255

Asp Glu Gln Lys Arg Cys Trp Thr Ala Leu Gln Arg Ile Asn Gln Ser
260 265 270

Gln Lys Asp Ile Gln Arg Ala His Asp Arg Glu Ala Ser Gln Arg Ala
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Cys Glu Gly Thr Glu Met Asp Cys Ala Glu Arg Gln Gln Leu Glu Lys
290 295 300

Asp Leu Arg Arg Gln Leu Lys Ser Met Gln Glu Trp Ile Glu Met Arg
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Gly Thr Ile His Gln Gln Glu Lys Ala Trp Arg Lys Gln Asn Ala Lys
325 330 335

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340 345 350

Glu Gln Ser Leu Phe Tyr Arg Glu Tyr Lys Glu Lys Tyr Leu Ser Gln
355 360 365

Lys Leu Asp Met Gln Lys Ile Leu Gln Glu Val Asn Ala Glu Lys Ser
370 375 380

Glu Lys Ala Cys Leu Glu Ser Leu Val His Asp Tyr Glu Lys Gln Leu
385 390 395 400

Glu Gln Lys Asp Ala Asn Leu Lys Lys Ala Ala Ala Val Trp Glu Glu
405 410 415

Glu Leu Gly Lys Gln Gln Gln Glu Asp Tyr Glu Gln Thr Gln Glu Ile
420 425 430

Arg Arg Leu Ser Thr Phe Ile Leu Glu Tyr Gln Asp Ser Leu Arg Glu
435 440 445

Ala Glu Lys Val Glu Lys Asp Phe Gln Glu Leu Gln Gln Arg Tyr Ser
450 455 460

Arg Leu Gln Glu Glu Lys Gln Val Lys Glu Lys Ile Leu Glu Glu Ser
465 470 475 480

Met Asn His Phe Ala Asp Leu Phe Glu Lys Ala Gln Lys Glu Asn Met
485 490 495

Ala Tyr Lys Lys Lys Leu Ala Asp Leu Glu Gly Ala Ala Ala Pro Thr
500 505 510

Glu Ile Gly Glu Asp Asp Asp Trp Val Leu Thr Asp Ser Ala Ser Leu
515 520 525

Ser Gln Lys Lys Ile Arg Glu Leu Val Glu Glu Asn Gln Glu Leu Leu
530 535 540

Lys Ala Leu Ala Phe Lys Ser Asn Glu Leu Thr Gln Leu Val Ala Asp
545 550 555 560

Ala Val Glu Ala Glu Lys Glu Ile Ser Lys Leu Arg Glu His Ile Glu
565 570 575

Glu Gln Lys Glu Gly Leu Arg Ala Leu Asp Lys Met His Ala Gln Ala
580 585 590

Ile Lys Asp Cys Glu Ala Ala Gln Arg Lys Cys Cys Asp Leu Glu Ser
595 600 605

Leu Leu Ser Pro Val Arg Glu Asp Ala Gly Met Arg Phe Glu Leu Glu
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Tyr Asp Glu Gly Phe Arg Asn Phe Ala Ser Ser Lys Val Thr Gln Ala
35 40 45

gta gtt tca gaa gaa aaa gtc ata gaa aag cct gta gtc gca gaa gtg 192
Val Val Ser Glu Glu Lys Val Ile Glu Lys Pro Val Val Ala Glu Val
50 55 60

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Pro Ser Arg Pro Ile Ala Lys Glu Thr Leu Ala Ala Gln Phe Ile Glu
65 70 75 80

agt aag ccg gtt att gta acc aca cca ccc gtg cct gtt gtt agc gaa 288
Ser Lys Pro Val Ile Val Thr Thr Pro Pro Val Pro Val Val Ser Glu
85 90 95

acc cca gaa gtg cct act gtg gca gtt ccg cct cag cct gtt cgt gag 336
Thr Pro Glu Val Pro Thr Val Ala Val Pro Pro Gln Pro Val Arg Glu
100 105 110

aca gta aaa gag gaa caa gct cct tat gct act gtt gta gtg aaa aaa 384
Thr Val Lys Glu Glu Gln Ala Pro Tyr Ala Thr Val Val Val Lys Lys
115 120 125

gga gat ttt ctc gaa cgc att gcg aga gca aat cat act acc gtt gca 432
Gly Asp Phe Leu Glu Arg Ile Ala Arg Ala Asn His Thr Thr Val Ala
130 135 140

aaa ttg atg cag atc aat gat ctt acc acc acc caa ctt aaa att ggt 480
Lys Leu Met Gln Ile Asn Asp Leu Thr Thr Thr Gln Leu Lys Ile Gly
145 150 155 160

cag gtc atc aaa gtc cct acg tct caa gat gtc agc aac gaa aaa act 528
Gln Val Ile Lys Val Pro Thr Ser Gln Asp Val Ser Asn Glu Lys Thr

                    165   170   175

cct caa aca cag acc gca aac cct gaa aat tat tat atc gtc caa gaa   576
Pro Gln Thr Gln Thr Ala Asn Pro Glu Asn Tyr Tyr Ile Val Gln Glu
            180   185   190

ggg gat agc ccg tgg aca ata gca ttg cgt aac cat att cga ttg gat   624
Gly Asp Ser Pro Trp Thr Ile Ala Leu Arg Asn His Ile Arg Leu Asp
        195   200   205

gat ttg cta aaa atg aat gat ctc gat gaa tat aaa gcc cgg cgc ctt   672
Asp Leu Leu Lys Met Asn Asp Leu Asp Glu Tyr Lys Ala Arg Arg Leu
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Tyr Asp Glu Gly Phe Arg Asn Phe Ala Ser Ser Lys Val Thr Gln Ala
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Val Val Ser Glu Glu Lys Val Ile Glu Lys Pro Val Val Ala Glu Val
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Pro Ser Arg Pro Ile Ala Lys Glu Thr Leu Ala Ala Gln Phe Ile Glu
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Ser Lys Pro Val Ile Val Thr Thr Pro Pro Val Pro Val Val Ser Glu
                85   90   95

Thr Pro Glu Val Pro Thr Val Ala Val Pro Pro Gln Pro Val Arg Glu
            100   105   110

Thr Val Lys Glu Glu Gln Ala Pro Tyr Ala Thr Val Val Val Lys Lys
        115   120   125

Gly Asp Phe Leu Glu Arg Ile Ala Arg Ala Asn His Thr Thr Val Ala
130 135 140

Lys Leu Met Gln Ile Asn Asp Leu Thr Thr Thr Gln Leu Lys Ile Gly
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Gln Val Ile Lys Val Pro Thr Ser Gln Asp Val Ser Asn Glu Lys Thr
165 170 175

Pro Gln Thr Gln Thr Ala Asn Pro Glu Asn Tyr Tyr Ile Val Gln Glu
180 185 190

Gly Asp Ser Pro Trp Thr Ile Ala Leu Arg Asn His Ile Arg Leu Asp
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU01/01021

A.	**CLASSIFICATION OF SUBJECT MATTER**
Int. Cl. ^{7}:	C12N 15/30

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
SEE ELECTRONIC DATABASES (BELOW)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
SEE ELECTRONIC DATABASES (BELOW)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WPIDS Medline CA: chlamydia, pyk, npld, cpn0585, ompA ompB, hsp60, persistent, lytic, intracellular, gene expression, lipopolysaccharide biosynthesis, vaccine, therapy, prophylactic, immunogenic, immunopotentiate.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	Mathews S et al. Differential expression of ompA, ompB, pyk, nlpD and Cpn0585 genes between normal and interferon-gamma treated cultures of *Chlamydia pneumoniae*. Microbial Pathogenesis. (June 2001). **30**(6): 337-45.	1-41
X	Gerard HC et al. Viability and gene expression in *Chlamydia trachomatis* during persistent expression of cultured human monocytes. Med Microbiol Immunol. 1998.. **187**: 115-120	1-41
X	Beatty WL et al. Morphologic and antigenic characterization of interferon gamma-mediated persistent *Chlamydia trachomatis* infection *in vitro*. Proc Natl Acad Sci USA. May 1 1993. **90**(9): 3998-4002.	1-41

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 November 2001	- 7 NOV 2001
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized officer **Gillian Allen** Telephone No : (02) 6283 2266

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Beatty W L et al. Immunoelectron-microscopic quantitation of differential levels of chlamydial proteins in a cell culture model of persistent *Chlamydia trachomatis* infection. Infection and Immunity. 1994. **62**(9): 4059-62.	1-41
X	Beatty W L et al. Reactivation of persistent *Chlamydia trachomatis* infection in cell culture. Infection and Immunity. 1995. **63**(1): 199-205.	1-41
X	WO 99/27105 A2 (GENSET) 3 June 1999.	109-125
X	WO 99/28475 A2 (GENSET) 10 June 1999	109-125
X	WO 00/03731 A2 (SPECTRUM MEDICAL SCIENCES LTD) 27 January 2000	109, 110, 112-117,120-125
X	WO 98/10789 A1 (CONNAUGHT LABORATORIES LTD) 19 March 1998	109, 110, 112-117,120-125
P, X	Penttila T et al. Immunity to *Chlamydia pneumoniae* induced by vaccination with DNA vectors expressing a cytoplasmic protein (Hsp60) or outer membrane proteins (MOMP and Omp2). Vaccine. 2001. **19**: 1256-1265	109-125
X Y	Read TD et al. Genome sequences of *Chlamydia trachomatis* MoPn and *Chlamydia pneumoniae* AR39. Nuc Acids Res. March 2000. **28**(6): 1397-1406.	109-123 124-125
X	Sanchez-Campillo M et al. Identification of immunoreactive proteins of *Chlamydia trachomatiss* by Western blot analysis of a two-dimensional electorophoresis map with patient sera. Electrophoresis. 1999. **20**: 2269-2279.	109, 110, 112-117,120-125
X	Brunham RC et al. *Chlamydia trachomatis* antigens: role in immunity and pathogenesis. Infectious Agents and Diseases. 1994. **3**(5): 3218-3233	109, 110, 112-117,120-125

Supplemental Box
(To be used when the space in any of Boxes I to VIII is not sufficient)

Continuation of Box No: II

Unity of Invention (cont'd)

At least some of the genes of claim 1, and their encoded proteins, are known, therefore they cannot provide a special technical feature that unifies the different inventions according to Rules 13.1 and 13.2 of the PCT. The expression "special technical features" is defined in Rule 13.2 as meaning those technical features that define a contribution which each of the inventions, considered as a whole, makes over the prior art.

There is further *a postiori* lack of unity between the genes/proteins that unite the separate inventions. Search of the claims has disclosed that OmpA, Hsp60 and gseA are already known to express at different levels in the persistent and lytic phase of *Chlamydia*. Thus the suggestion that the proteins/genes of the invention form a unified group because they share this feature is not valid. Thus differential expression between persistent and lytic phases can no longer be considered a special technical feature of the invention, and each of the claimed proteins becomes a single invention. However, the ISA has chosen not to take further unity objections on this basis.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/AU01/01021

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report	Patent Family Member
WO 99/27105 A2	AU 11702/99
	BR 9814878
	EP 1032674
WO 99/28475 A2	AU 12545/99
	BR 9814912
	EP 1032676
WO 00/03731 A2	AU 52143/99
WO 98/10789 A1	AU 41958/97
	EP 0957935

END OF ANNEX

Box I **Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [ ] Claims Nos :

because they relate to subject matter not required to be searched by this Authority, namely:

2. [X] Claims Nos : 51-108

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

The scope of the "agents" of the claims is indeterminate. Agents that alter gene expression include DNA binding molecules, activators, repressors, products of enzyme synthesis and antibiotics, among the most obvious candidates. Agents that alter the functional activity of a protein include protein denaturants, enzyme inhibitors, antibodies, buffer components, enzyme co-factors, proteases, etc. The agents are not limited to the technical features that define the invention, namely Chlamydial proteins and the genes that encode them.

3. [ ] Claims Nos :

because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box II **Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. **Invention no 1**, defined by claims 1-41 is to a method of detecting a Chlamydial organism in its persistent phase by detecting a change of expression of a range of genes, or of genes belonging to their respective biosynthetic pathways, when the expression level is compared to that of the organism in its lytic phase.

2. **Invention no** 2, defined by claims 42-50 is to a method of screening for an agent that modulates the expression of any of the genes defined in claim 1, or the levels or functional activity of their expressed proteins. The method essentially consists of providing the modulating agent, and detecting a change (or otherwise) in gene expression, levels or functional activity of their expressed proteins.

3. **Invention no 3**, defined by claims 109-125 is to "immunopotentiating compositions" comprising any antigen associated with the persistent phase of a Chlamydial organism, preferably antigens that are all or part of the peptides expressed by the genes of claim 1.

Continued in Supplemental box

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims
2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. [X] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:**1-41 and 109-125**
4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[X] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.